

## Supplementary Appendix Hoogman *et al.*

Supplement to: Subcortical brain volume differences of participants with ADHD across the lifespan: an ENIGMA collaboration

Content:

- sMethods
- sTable 1. Additional information on procedures and methods at the participating sites.
- sTable 2. Clinical characteristics and IQ for cases and controls per cohort.
- sTable 3. Results of the mega-analysis of subcortical left and right brain volumes.
- sTable 4. Results of the mega-analysis with and without the addition of FreeSurfer versions as covariate
- sTable 5. The contribution of handedness to the mega-analysis model
- sTable 6. Meta-analysis: Effect sizes (Cohen's  $d$ ) for the mean volume of each brain region, after controlling for age, sex, and intracranial volume
- sTable 7. Linear effects of age and age\*diagnosis
- sTable 8. The results of the fractional polynomial analysis.
- sTable 9. Results of the meta-analysis of the correlation between ADHD symptom scores and subcortical volumes and ICV that were significantly different in cases compared to controls.
- sTable 10. Effect of comorbid disorders on subcortical volumes and ICV
- sFigure1. Boxplots of the bilateral subcortical volumes.
- sFigure2. Forest plots: results of the meta-analysis of case-control differences in subcortical brain volume.
- sFigure3. Number of subjects per age bin.
- sFigure4. Results of the fractional polynomial analysis for the subcortical brain volumes.
- sFigure5. Forest plot: result of the meta-analysis of the correlation between total number of ADHD symptoms and caudate volume.

## **Methods**

### *Explaining mega- and meta-analysis*

By mega-analysis we refer to the method of pooling all available individual data from all cohorts and analyzing the main effects in one single analysis. In the meta-analysis, we are first determining the main effects in each sample separately and then combine only those summary statistics in one meta-analysis. The advantage of the mega-analysis over the meta-analysis is the additive increase in degrees of freedom thereby increasing power, whereas the advantage of the meta-analysis is that site effects can be rigorously eliminated.

### *Imaging quality control methods*

The following FreeSurfer labels were extracted: Left-Thalamus-Proper, Right-Thalamus-Proper, Left-Caudate, Right-Caudate, Left-Putamen, Right-Putamen, Left-Pallidum, Right-Pallidum, Left-Hippocampus, Right-Hippocampus, Left-Amygdala, Right-Amygdala, Left-Accumbens-area, Right-Accumbens-area. Next, by running a script called make\_pngsFS.m segmentations were projected onto the t1 brain scan. These images were all inspected using SurfScan. Bad segmentations were excluded for further analysis. Statistical outliers were identified when a volume was smaller or larger than 1.5 times the interquartile range. Scripts and protocols are available on (<http://enigma.ini.usc.edu/protocols/imaging-protocols/>).

### *Statistical framework of the meta-analysis*

The R-package “metaphor” (version 1.9-1<sup>1</sup>) was used to perform an inverse variance-weighted, random-effects meta-analysis, in accordance with other ENIGMA Working Groups<sup>2,3</sup>. A random-effects model was chosen, as we expected heterogeneity of effect sizes across samples. We fitted all random-effects models using the restricted maximum likelihood method (REML<sup>4</sup>). The model includes diagnosis (case=1, control =0), age, sex and ICV. In the meta-analysis of ICV, ICV was omitted as covariate. To calculate Cohen’s *d* effect size estimates, adjusted for age, sex, and ICV, we used the *t*-statistic from the Diagnosis predictor in the equation<sup>5</sup> for each sample separately. We also ran the model excluding the ICV term. To correct for testing 8 brain volumes, we used Bonferroni correction (significance threshold *p*=0.006).

### *Extended modeling of age*

We calculated a ‘moving’ average for the predicted volumes across age, incorporating sex, ICV, and site. The moving average was obtained by averaging brain volumes using a 5-year sliding window with 1-year increments. Secondly, we used fractional polynomials (Stata/SE 11.2, StataCorp LP, Texas, USA) to search for the optimal model of age for each volume using one- and two-term curvilinear models. The fractional polynomials were calculated separately for the participants with ADHD and healthy controls. These models all included age, sex, ICV, and site. The best-fitting model was chosen among the 8 possible one-term models and among 44 possible two-term models (for the following powers: -2, -1, -0.5, 0, 0.5, 1, 2, 3). Deviance for the linear model versus the one- and two-term models was calculated to identify the best model for each volume and participant group<sup>6</sup>.

### *Clinical measures and subcortical volume and ICV*

As ADHD symptom scores from different sites had been assessed using varying instruments and raters (see sTable1 and 3), we performed a meta-analysis of the correlation between ADHD symptom scores and subcortical volumes and ICV, controlling for age, gender, and ICV (the latter only in the subcortical volume analyses), using Medcalc v12.5 (MedCalc Software, Ostend, Belgium). We restricted this random-effects meta-analysis to cases, because healthy controls had often been selected based on low ADHD symptom scores.

To explore possible effects of the most frequent co-morbid disorders (see sTable 1 & 3 for instruments used and prevalence in our cohorts) on the subcortical volumes and ICV, we first scored the psychiatric disorders as a ‘positive lifetime history’ or ‘negative lifetime history’ for all subjects based on the information we had from the clinical interviews. Subsequently, we added the following terms to the mega-analysis model: presence/absence of a psychiatric disorder, presence/absence of depression, presence/absence of anxiety disorder, presence/absence of substance use disorder. We did this in separate analyses because of collinearity

**sTable 1. Additional information on procedures and methods at the participating sites.**

Sample	Reference	Free-Surfer version	Field strength of the MRI scanner	Medication withheld during imaging	Washout period medication before imaging	Classification system for diagnosis†	Instrument for comorbidity assessment	Instrument for symptom rating	IQ instrument
ADHD-WUE	Conzelmann et al., Biol Psychiatry 2009	5.3	1.5 Tesla	Partly	hours to days	DSM-IV	SCID1	DSM-IV interview	MWT-B
ADHD-DUB1	McCarthy et al., JAMA Psych 2013	5.3	3 Tesla	Yes	48 h	DSM-IV	SCID1	Conners Adult ADHD rating scale observer	Verbal Comprehension, Perceptual Reasoning, Working Memory and Processing Speed subtests of WAIS-IV
ADHD-DUB2	Frodl et al., 2010 Amico et al., 2011	5.3	1.5 Tesla	No	no washout	DSM-IV	SCID1	Conners Adult ADHD rating scale observer	NA
ADHD-Mattos	Cocchi et al., J Neuroscience 2012	5.1	3 Tesla	not medication on	not applicable	DSM-IV	MINI	K-SADS adapted for adults	WASI
ADHD200-KKI	<a href="http://fcon_1000.projects.nitrc.org/indi/adhd200/">http://fcon_1000.projects.nitrc.org/indi/adhd200/</a>	5.3	1.5 Tesla	unknown	unknown	DSM-IV	NA	Conners Parent Rating Scale Revised Long version	WISC-IV
ADHD200-NYU	<a href="http://fcon_1000.projects.nitrc.org/indi/adhd200/">http://fcon_1000.projects.nitrc.org/indi/adhd200/</a>	5.3	3 Tesla	yes	24h	DSM-IV	NA	Conners Parent Rating Scale Revised Long version	WASI
ADHD200-Peking	<a href="http://fcon_1000.projects.nitrc.org/indi/adhd200/">http://fcon_1000.projects.nitrc.org/indi/adhd200/</a>	5.3	3 Tesla	yes	48h	DSM-IV	NA	ADHD rating scale	WISCC-R
ADHD200-OHSU	<a href="http://fcon_1000.projects.nitrc.org/indi/adhd200/">http://fcon_1000.projects.nitrc.org/indi/adhd200/</a>	5.3	3 Tesla	yes	24-48h	DSM-IV	NA	Conners rating scale 3rd edition	Block Design, Vocabulary and Information subtests of WISC-IV

ADHD-UKA	Vloet et al., 2010, Konrad et al., 2006, Herpertz 2008, Hubner et al., 2008, Krinzinger et al., 2011	5.3	3 Tesla	Yes	48h	ICD10	K-SADS and German K-Dips	German Parental and Teacher Report on ADHD	CPM (N = 30)/WASI (N = 49)/WISC-IV (N = 14)
Bergen-adultADHD	Dramsdahl et al., Front Psychiatry 2011	5.3	3 Tesla	Partly	48h	ICD-10 or DSM-IV	NA	NA	WASI
Bergen-SVG	-	5.3	3 Tesla	not medication on	not applicable	DSM-IV	K-SADS-PL	K-SADS PL	WISC-IV

DAT-London	Paloyelis et al., JAACAP 2013	5.3	3 Tesla	Yes	48h	DSM-IV	NA	NA	Vocabulary, Similarities, Picture Completion and Block Design subtests of WISC/WAIS
IMpACT-NL	Hoogman et al., AMJP 2011	5.3	1.5 Tesla	Yes	24h	DSM-IV	SCID1&2	DSM-IV interview	Vocabulary and block design subtests of WAIS
MGH	Seidman et al., Biol. Psychiatry 2011	5.1	1.5 Tesla	Yes	24h	DSM-IV	SCID1	DSM-IV interview	Vocabulary and block design subtests of WAIS
NICHE	de Zeeuw et al , PloS One 2012	5.1	1.5 Tesla	partly	0-24h	DSM-IV	DISC-IV	NA	Vocabulary and block design subtests of WISC-III
NYU ADHD	-	5.3	3 Tesla	Yes	24h	DSM-IV	SCID	NA	WASI
UAB-ADHD	-	5.3	3 Tesla	Yes	48h	DSM-IV	NA	NA	WISC
ZI-CAPS	-	5.3	3 Tesla	Yes	48h	DSM-IV	ODD and CD with structured clinical interview	Kiddie SADS	Subscales of HAWIK-IV
ADHD-Rubia	Lim et al, Psychological Medicine 2015	5.3	3 Tesla	Yes	48h	DSM-IV	Co-morbid disorders were exclusion criteria	SDQ for Hyperactive impulsive symptoms and Conners Parent Rating scale revised for Inattentive symptoms	WASI
NeuroImage-ADAM	von Rhein et al, ECAP 2014	5.3	1.5 Tesla	Yes	48h	DSM-IV	K-SADS-PL	Algorithm Von Rhein, see reference	Vocabulary and block design subtest of WAIS/WISC
NeuroImage-NIJM	von Rhein et al, ECAP 2014	5.3	1.5 Tesla	Yes	48h	DSM-IV	K-SADS-PL	Algorithm Von Rhein, see reference	Vocabulary and block design subtest of WAIS/(WISC

NIH	Shaw et al, Biological psychiatry	5.1	1.5 Tesla	Yes	36h	DSM-IV	DICA	NA	Subtests of WISC
MTA	Tamm et al, Drug and Alc. Dep 2013	5.3	3 Tesla	Yes	24h	DSM-IV	NA	NA	WISC-III full version (N = 87)/subtests of WISC-III (N = 42)

†All adult ADHD cases were (retrospectively) diagnosed with ADHD in childhood.

SCID: Structured Clinical Interview for DSM disorders, MINI: M.I.N.I. International Neuropsychiatric Interview, K-SADS: Kiddie Schedule for Affective Disorders and Schizophrenia; K-DIPS: Kinder Diagnostische Interview bei psychischen Störungen, DISC-IV: Diagnostic Interview Schedule for Children, K-SADS-PL; Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime; DICA: Diagnostic Interview for Children and Adolescents. SDQ: Strengths and Difficulties questionnaire. MWT-B: Mehrfachwahl-Wortschatz-Intelligenz-Test, WAIS-IV: Wechsler Adult Intelligence Scale Fourth Edition, WASI: Weschler Abbreviated Scale of Intelligence, WISC-IV: Wechsler Intelligence Scale for Children Fourth Edition, WISCC-R: Wechsler Intelligence Scale for Chinese Children-Revised, CPM: Colored Progressive Matrices, WAIS-III: Wechsler Adult Intelligence Scale Thirth Edition, WISC-III: Wechsler Intelligence Scale for Children Thirth Edition, HAWIK-IV: Hamburg-Weschsler-Intelligentztest fuer Kinder-IV

**sTable 2. Clinical characteristics and IQ for cases and controls per cohort**

Cohort	ADHD symptom score in cases only*	N Lifetime co-morbid disorder present*	N Lifetime co-morbid depression present*	N Lifetime co-morbid anxiety*	N Lifetime co-morbid SUD*	IQ*
	Mean (SD; n)	Yes/No/Unknown	Yes/No/Unknown	Yes/No/Unknown	Yes/No/Unknown	Mean (SD; n)
ADHD-WUE cases	13·1 (2·6;37)	41/19/2	30/30/2	14/45/3	7/52/3	117 (16;56)
ADHD-WUE controls	-	3/53/0	3/53/0	0/56/0	0/56/0	114 (14;50)
ADHD-DUB1 cases	119·0 (22·9;34)	17/19/0	0/32/4	0/32/4	15/19/2	113 (12;36)
ADHD-DUB1 controls	-	8/31/0	0/39/0	1/38/0	9/29/1	103 (13;33)
ADHD-DUB2 cases	30·5 (9·1;20)	7/13/0	7/13/0	1/19/0	0/20/0	NA
ADHD-DUB2 controls	-	0/0/0	0/0/0	0/0/0	0/0/0	NA
ADHD-Mattos cases	12·4 (2·4;17)	8/9/0	3/14/0	7/10/0	3/14/0	114 (8;17)
ADHD-Mattos controls	-	0/0/0	0/0/0	0/0/0	0/0/0	NA
ADHD200-KKI cases	146·1 (19·6;22)	0/0/25	0/0/25	0/0/25	0/0/25	112 (10;69)
ADHD200-KKI controls	-	0/0/69	0/0/69	0/0/69	0/0/69	107 (15;25)
ADHD200-NYU cases	139·8 (17·4;148)	0/0/151	0/0/151	0/0/151	0/0/151	111 (14;102)
ADHD200-NYU controls	-	0/0/109	0/0/109	0/0/109	0/0/109	106 (14;146)
ADHD200-Peking cases	50·5 (8·6;95)	0/0/102	0/0/102	0/0/102	0/0/102	118 (13;142)
ADHD200-Peking controls	-	0/0/143	0/0/143	0/0/143	0/0/143	106 (13;102)
ADHD200-OHSU cases	143·1 (18·6;36)	0/0/42	0/0/42	0/0/42	0/0/42	116 (13;67)
ADHD200-OHSU controls	-	0/0/67	0/0/67	0/0/67	0/0/67	110 (14;42)
ADHD-UKA cases	13·8 (1·8;102)	34/67/1	0/101/1	6/95/1	0/101/1	110 (13;79)

ADHD-UKA controls	-	0/0/79	0/0/79	0/0/79	0/0/79	102 (12;85)
Bergen-adultADHD cases	NA	0/0/38	0/0/38	0/0/38	0/0/38	116 (9;37)
Bergen-adultADHD controls	-	0/0/43	0/0/43	0/0/43	0/0/43	111 (14;29)
Bergen-SVG cases	9·6 (3·6;25)	0/0/25	0/0/25	0/0/25	0/0/25	96 (9;29)
Bergen-SVG controls	-	0/0/29	0/0/29	0/0/29	0/0/29	97 (12;24)
DAT-London cases	NA	0/0/27	0/0/27	0/0/27	0/0/27	114 (11;29)
DAT-London controls	-	0/0/29	0/0/29	0/0/29	0/0/29	109 (11;27)
IMpACT-NL cases	12·9 (3·3;104)	79/46/0	57/68/0	25/100/0	22/103/0	110 (15;120)
IMpACT-NL controls	-	23/97/0	12/108/0	6/114/0	6/114/0	107 (15;125)
MGH-ADHD cases	9·4 (4·2;79)	61/18/0	46/33/0	17/62/0	38/41/0	113 (13;69)
MGH-ADHD controls	-	29/40/0	15/54/0	2/67/0	21/48/0	115 (13;78)
NICHE cases	NA	34/44/0	0/78/0	0/78/0	0/78/0	106 (13;80)
NICHE controls	-	0/80/0	0/80/0	0/80/0	0/80/0	102 (15;78)
NYU ADHD cases	NA	20/20/0	14/26/0	5/35/0	9/31/0	112 (11;39)
NYU controls	-	7/33/0	3/37/0	2/38/0	3/37/0	111 (12;39)
UAB-ADHD cases	NA	0/0/103	0/0/103	0/0/103	0/0/103	NA
UAB-ADHD controls	-	0/0/95	0/0/95	0/0/95	0/0/95	106 (16;13)
ZI-CAPS cases	8·8 (4·6;22)	0/0/22	0/0/22	0/0/22	0/0/22	120 (19;13)
ZI-CAPS controls	-	0/0/13	0/0/13	0/0/13	0/0/13	110 (16;22)
ADHD-Rubia cases	88·8 (11·4;36)	0/44/0	0/44/0	0/44/0	0/44/0	110 (11;33)

ADHD-Rubia controls	-	0/33/0	0/33/0	0/33/0	0/33/0	92 (12;41)
NeuroImage-ADAM cases	13·4 (3·0;97)	31/64/2	0/0/97	0/0/97	0/0/97	105 (13;85)
NeuroImage-ADAM controls	-	14/71/0	0/0/85	0/0/85	0/0/85	95 (14;97)
NeuroImage-NIJM cases	13·2 (2·8;139)	62/73/4	1/0/138	0/0/139	0/0/139	109 (14;39)
NeuroImage-NIJM controls	-	5/34/0	0/0/39	0/0/39	0/0/39	98 (15;139)
NIH cases	NA	0/0/251	0/0/251	0/0/251	0/0/251	108 (11;235)
NIH controls	-	0/0/251	0/0/251	0/0/251	0/0/251	108 (15;233)
MTA cases	NA	0/0/88	0/0/88	0/0/88	0/0/88	108 (22;40)
MTA controls	-	0/0/41	0/0/41	0/0/41	0/0/41	103 (15;87)

\*see for instruments used sTable 1, NA is Not Available

**sTable 3. Results of the mega-analysis of subcortical left and right brain volumes.**

	Side	p-value for <i>Diagnosis</i>	Cohen's <i>d</i>
Accumbens	Left	2.92x10 <sup>-9</sup>	-0.15
	Right	0.004	-0.10
Amygdala	Left	4.13x10 <sup>-8</sup>	-0.17
	Right	6.35x10 <sup>-8</sup>	-0.16
Caudate	Left	0.01	-0.09
	Right	0.0004	-0.13
Hippocampus	Left	0.005	-0.10
	Right	0.02	-0.08
Pallidum	Left	0.71	-0.01
	Right	0.91	0.00
Putamen	Left	0.0002	-0.13
	Right	0.0001	-0.14
Thalamus <sup>#</sup>	Left	0.81	-0.01
	Right	0.10	-0.06

<sup>#</sup>thalamus volume was not available from the NIH sample.

**sTable 4. Results of the mega-analysis with and without the addition of FreeSurfer versions as covariate**

	Model without FreeSurfer version		Model with FreeSurfer version	
	Cohen's d (90% CI)	p-value	Cohen's d (90% CI)	p-value
Accumbens	-0.15 (-0.22 - -0.08)	4.98x10 <sup>-9</sup>	-0.15 (-0.22 - -0.08)	5.34x10 <sup>-5</sup>
Amygdala	-0.19 (-0.26 - -0.11)	3.69x10 <sup>-7</sup>	-0.19 (-0.26 - -0.12)	3.45x10 <sup>-7</sup>
Caudate	-0.11 (-0.18 - -0.03)	0.001	-0.12 (-0.19 - -0.05)	0.001
Hippocampus	-0.11 (-0.18 - -0.03)	0.004	-0.10 (-0.18 - -0.03)	0.004
Pallidum	-0.00 (-0.07 - 0)	0.95	0.00 (-0.07 - 0.07)	0.93
Putamen	-0.14 (-0.21 - -0.07)	6.36x10 <sup>-9</sup>	-0.14 (-0.21 - -0.07)	7.32x10 <sup>-5</sup>
Thalamus	-0.03 (0.03 - -0.10)	0.39	-0.03 (-0.11 - 0.04)	0.37

**sTable5. The contribution of handedness to the mega-analysis model.**

Brain volume	p-value handedness in the model
Accumbens	0.81
Amygdala	0.46
Caudate	0.54
Hippocampus	0.36
Pallidum	0.99
Putamen	0.45
Thalamus	0.99

**sTable 6. Meta-analysis: Effect sizes (Cohen's  $d$ ) for the mean volume of each brain region, after controlling for age, sex, and intracranial volume.**

Brain volume	N Cases/Controls	Cohen's $d \pm SE$	p-value	95% CI	$I^2$
Accumbens	1650/1471	-0.11±0.05	0.04	(-0.21 - -0.00)	46%
Amygdala	1598/1463	-0.15±0.05	0.004**	(-0.26 - -0.05)	45%
Caudate	1660/1489	-0.11±0.04	0.006**	(-0.18 - -0.03)	10%
Hippocampus	1592/1436	-0.05±0.06	0.37	(-0.16 - 0.06)	52%
Pallidum	1651/1471	0.01±0.04	0.73	(-0.06 - 0.09)	8%
Putamen	1661/1497	-0.11±0.04	0.002**	(-0.19 - -0.04)	4%
Thalamus <sup>#</sup>	1406/1242	-0.02±0.04	0.60	(-0.11 - 0.06)	9%
ICV	1694/1513	-0.12±0.04	0.003**	(-0.19 - -0.004)	14%

\*\*significant at Bonferroni-corrected threshold (<0.006), <sup>#</sup>thalamus volume was not available from the NIH sample.  $I^2$  represents the percentage of the observed variation due to differences between samples. Data from 21 cohorts were included, two were excluded because of their patient-only design.

**sTable7. Linear effects of age and age\*diagnosis**

	p-value for the term ‘age’ in the model	p-value for the term ‘age*diagnosis’ in the model
Accumbens	4.70x10 <sup>-33</sup>	0.37
Amygdala	0.16	0.67
Caudate	2.95x10 <sup>-20</sup>	0.21
Hippocampus	0.28	0.03
Pallidum	2.62x10 <sup>-55</sup>	0.96
Putamen	1.30x10 <sup>-54</sup>	0.19
Thalamus	1.03x10 <sup>-7</sup>	0.32
ICV	0.004	0.10

**sTable 8. The results of the fractional polynomial analysis.**

	Participants with ADHD		Healthy controls	
Subcortical volume	Optimal model of age controlling for sex, ICV, sample	R <sup>2</sup>	Optimal model of age controlling for sex, ICV, sample	R <sup>2</sup>
Accumbens	Linear model of age	0.43	Linear model of age	0.48
Amygdala	2 term model of age (0,3)	0.48	1 term model of age (-2)	0.46
Caudate	Linear model of age	0.43	Linear model of age	0.32
Hippocampus	1 term model of age (-2)	0.53	2 term model of age (0,0)	0.48
Pallidum	Linear model of age	0.50	Linear model of age	0.52
Putamen	Linear model of age	0.54	2 term model of age (-1,-0)	0.50
Thalamus	2 term-model of age (-2,3)	0.61	2 term-model of age (-1,3)	0.49
ICV	2 term-model of age (0.5, 0.5)	0.43	2 term-model of age (0.5,1)	0.20

**Table 9. Results of the meta-analysis of the correlation between ADHD symptom scores and subcortical volumes and ICV that were significantly different in cases compared to controls.**

	Analysis in all cases				Analysis in all childhood cases			
	N	Correlation coefficient	95%CI	p-value random effects analysis	N	Correlation coefficient	95%CI	p-value random effects analysis
Accumbens	969	-0.02	-0.10 - 0.06	0.62	465	-0.07	-0.19 - 0.05	0.23
Amygdala	964	-0.04	-0.1 - 0.03	0.26	465	-0.02	-0.11 - 0.07	0.69
Caudate	975	0.08	0.02 - 0.14	0.02*	473	-0.07	-0.02 - 0.17	0.11
Hippocampus	969	0.0007	-0.06 - 0.07	0.84	472	-0.03	-0.12 - 0.06	0.49
Putamen	980	-0.01	-0.09 - 0.06	0.78	476	-0.06	-0.19 - 0.07	0.36
ICV	999	-0.01	-0.07 - 0.05	0.67	482	-0.06	-0.15 - 0.03	0.22

\*Also see sFigure5 for the Forest plot.

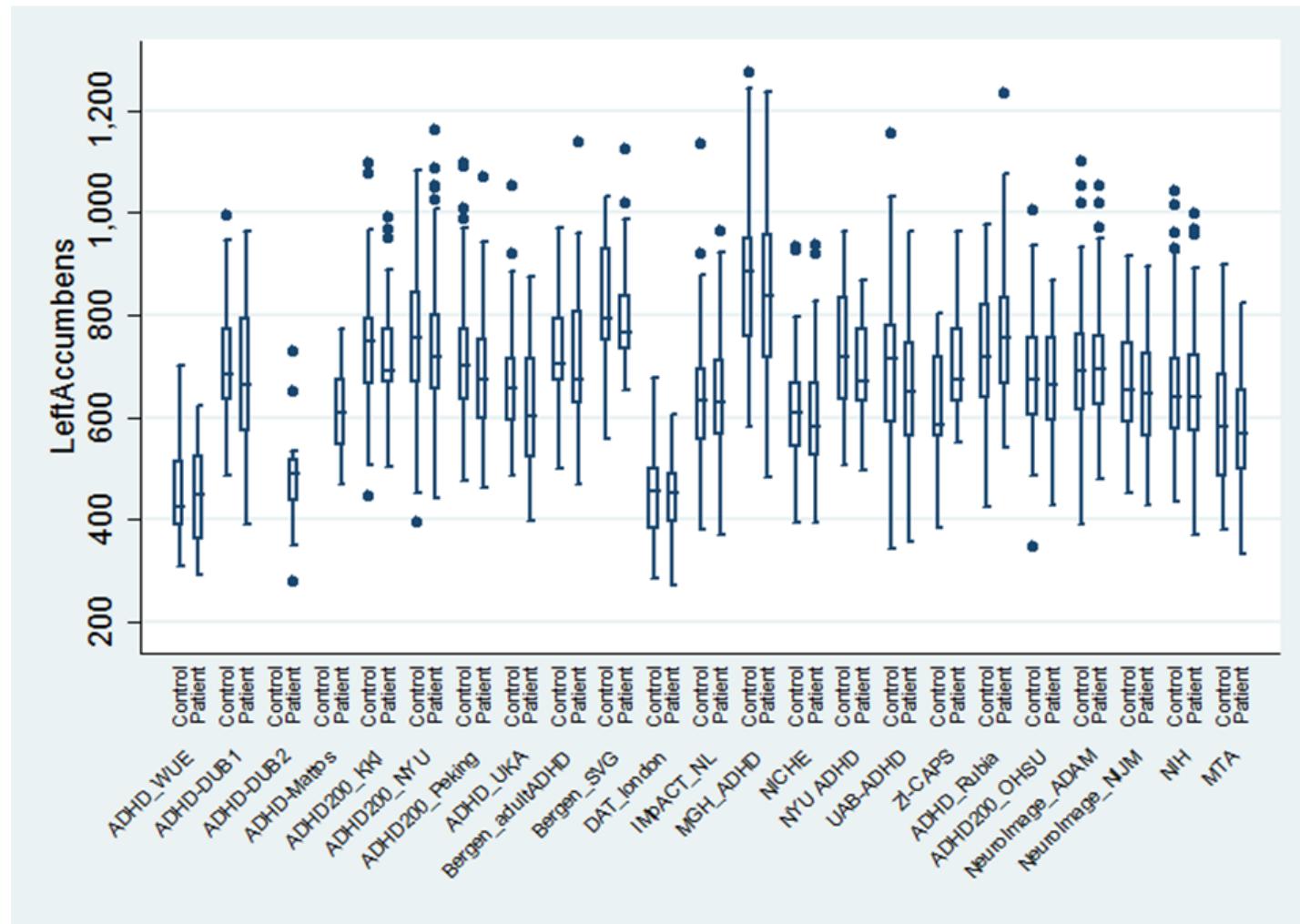
**sTable 10. Effect of comorbid disorders on subcortical volumes and ICV; displayed are p-values.**

	Any disorder	Depression/dysthymia	Anxiety	SUD
Accumbens	0.57	0.64	0.41	0.95
Amygdala	0.77	0.72	0.36	0.41
Caudate	0.88	0.60	0.40	0.33
Hippocampus	0.30	0.15	0.44	0.84
Putamen	0.06	0.10	0.18	0.75
ICV	0.83	0.30	0.99	0.76

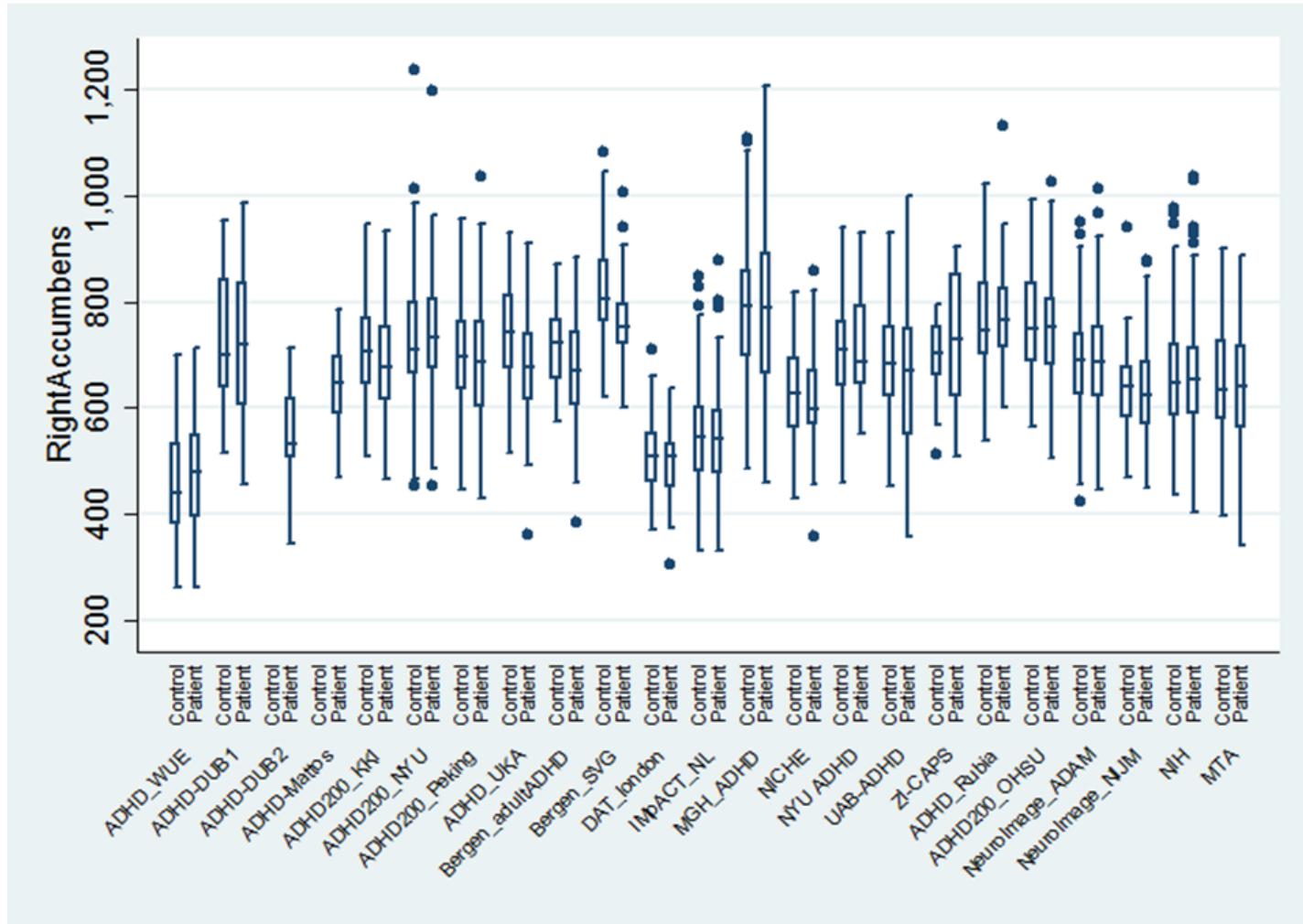
Displayed are the p-values for the variables ‘presence/absence of any psychiatric disorder’, ‘presence/absence of depression/dysthymia’, ‘presence/absence of anxiety disorder’, and ‘presence/absence of substance use disorder’ in the mega-analysis.

**sFigure1. Boxplots of the bilateral subcortical volumes.**

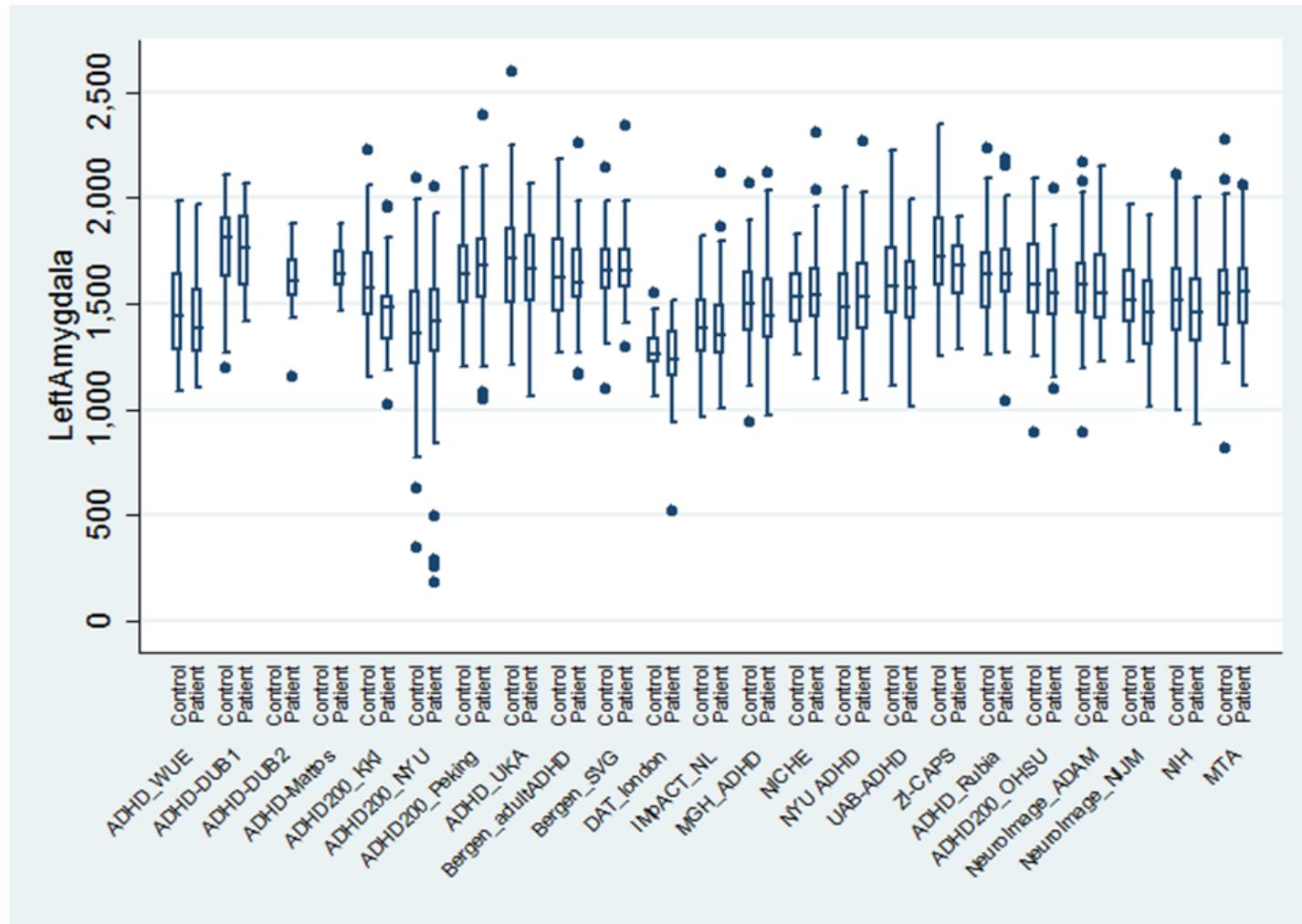
Boxplot for Left Accumbens in mm<sup>3</sup> per sample, including outliers (>+/-1,5 IQR)



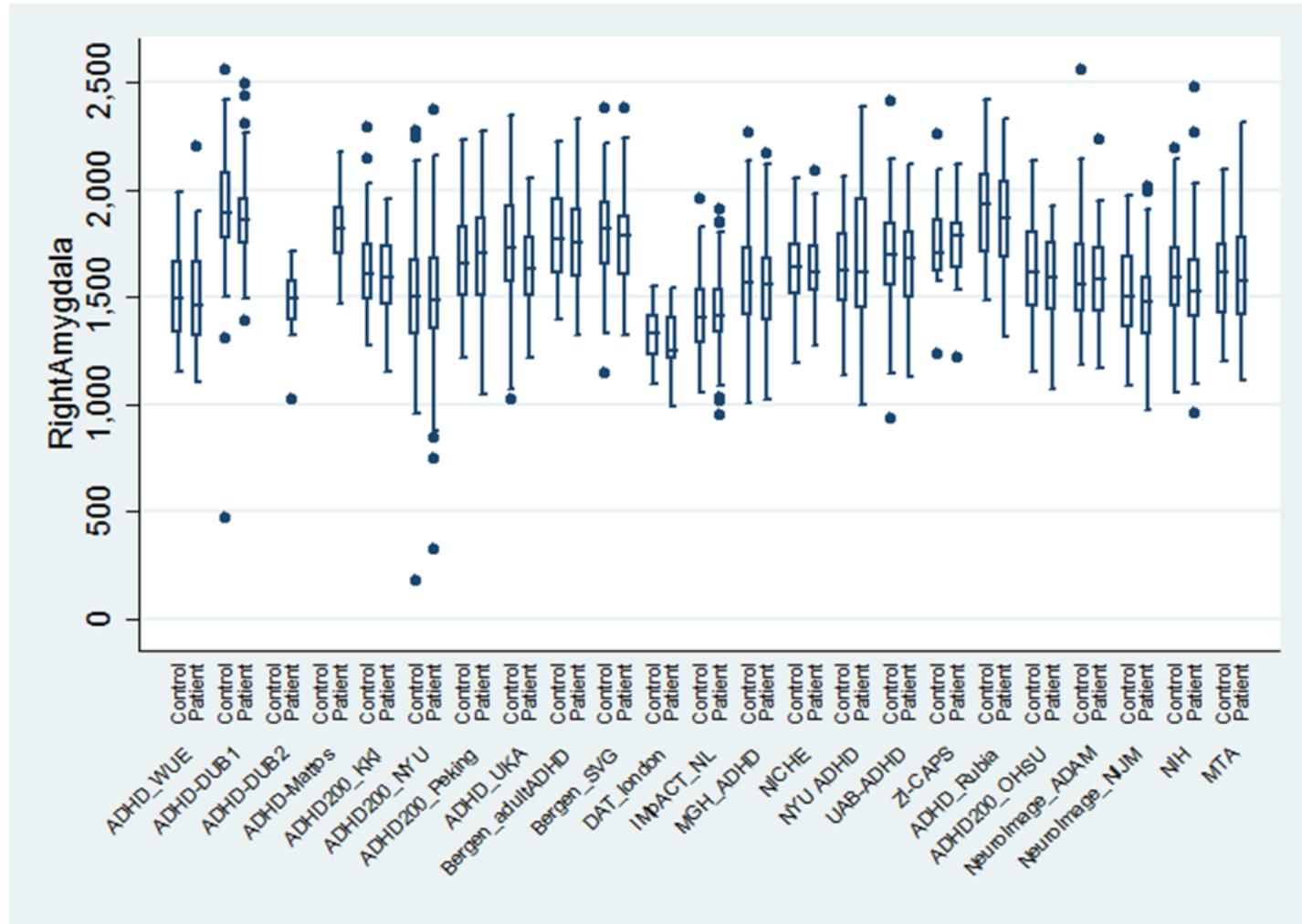
Boxplot for Right Accumbens in mm<sup>3</sup> per sample, including outliers (>+/-1,5 IQR)



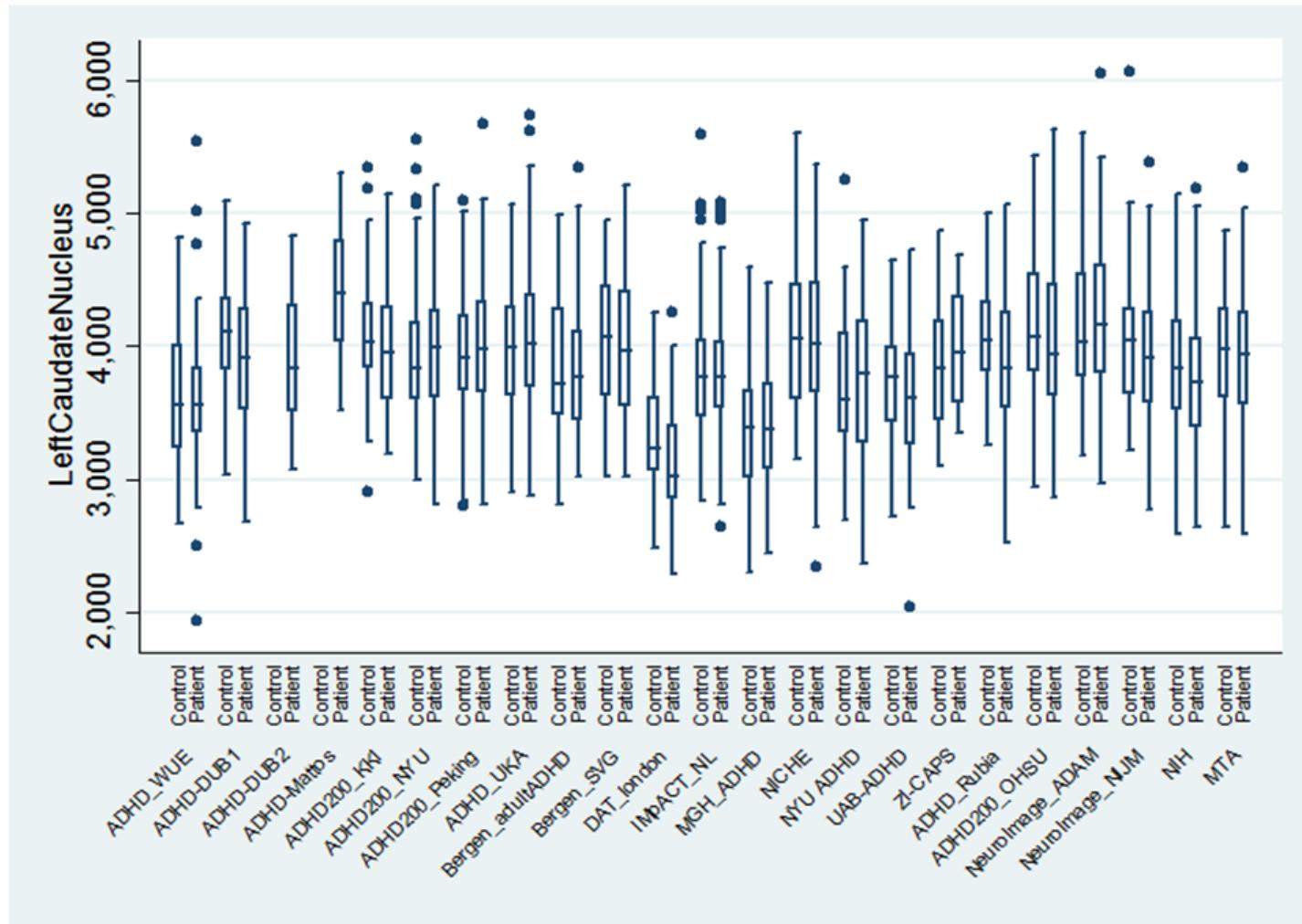
Boxplot for Left Amygdala in mm<sup>3</sup> per sample, including outliers (>+/-1,5 IQR)



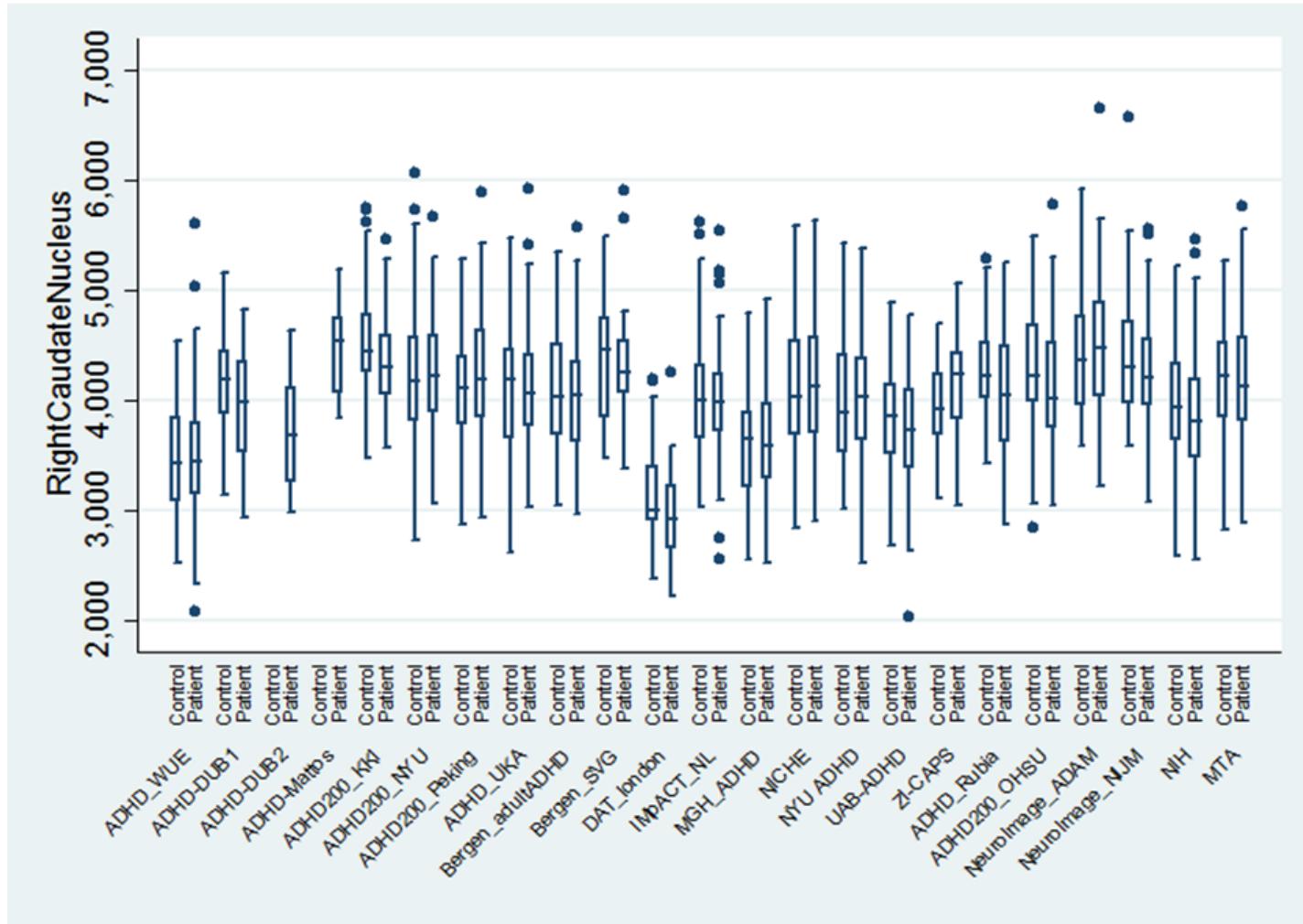
Boxplot for Right Amygdala in mm<sup>3</sup> per sample, including outliers (>+/-1,5 IQR)



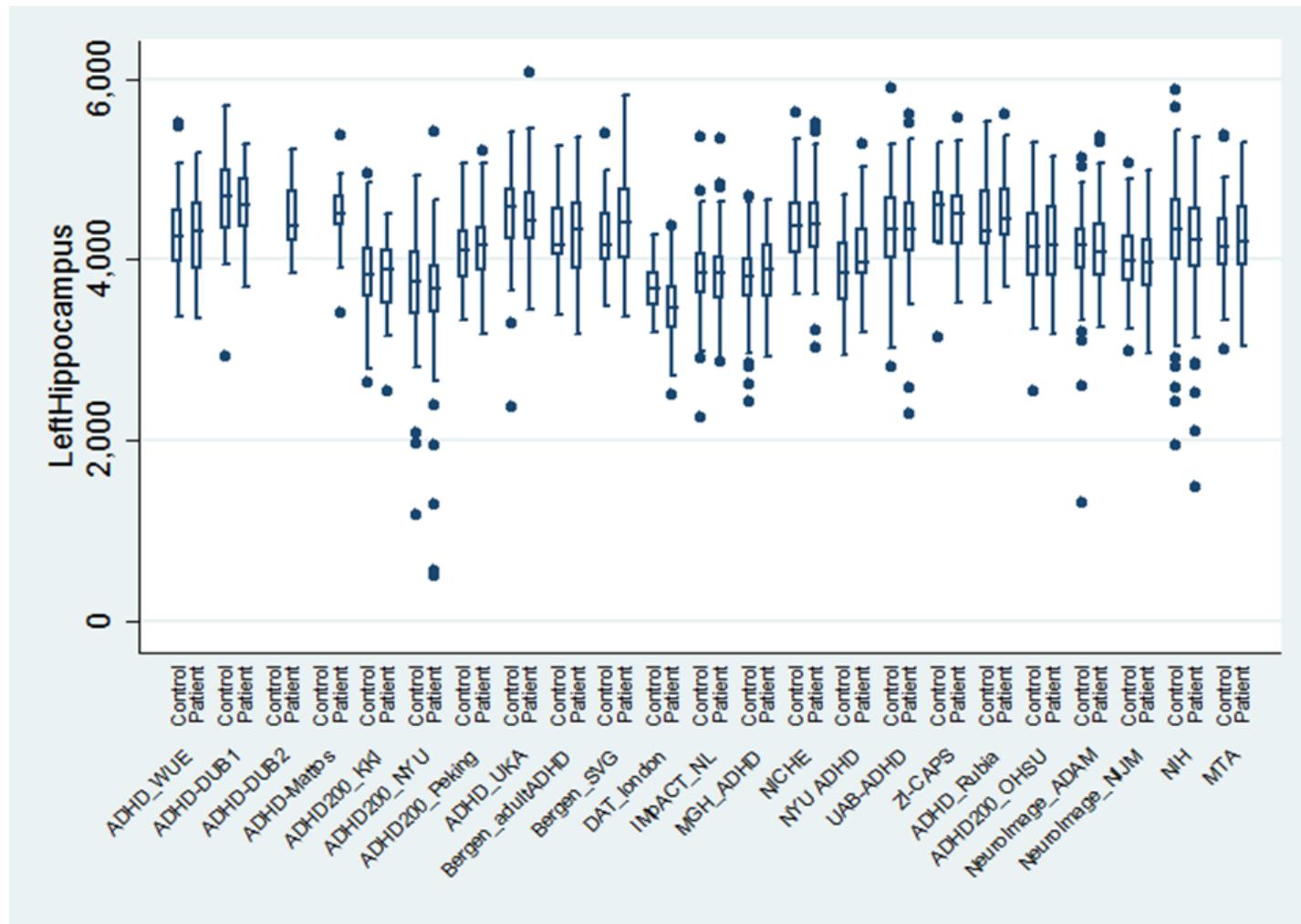
Boxplot for Left Caudate nucleus in mm<sup>3</sup> per sample, including outliers (>+/-1,5 IQR)



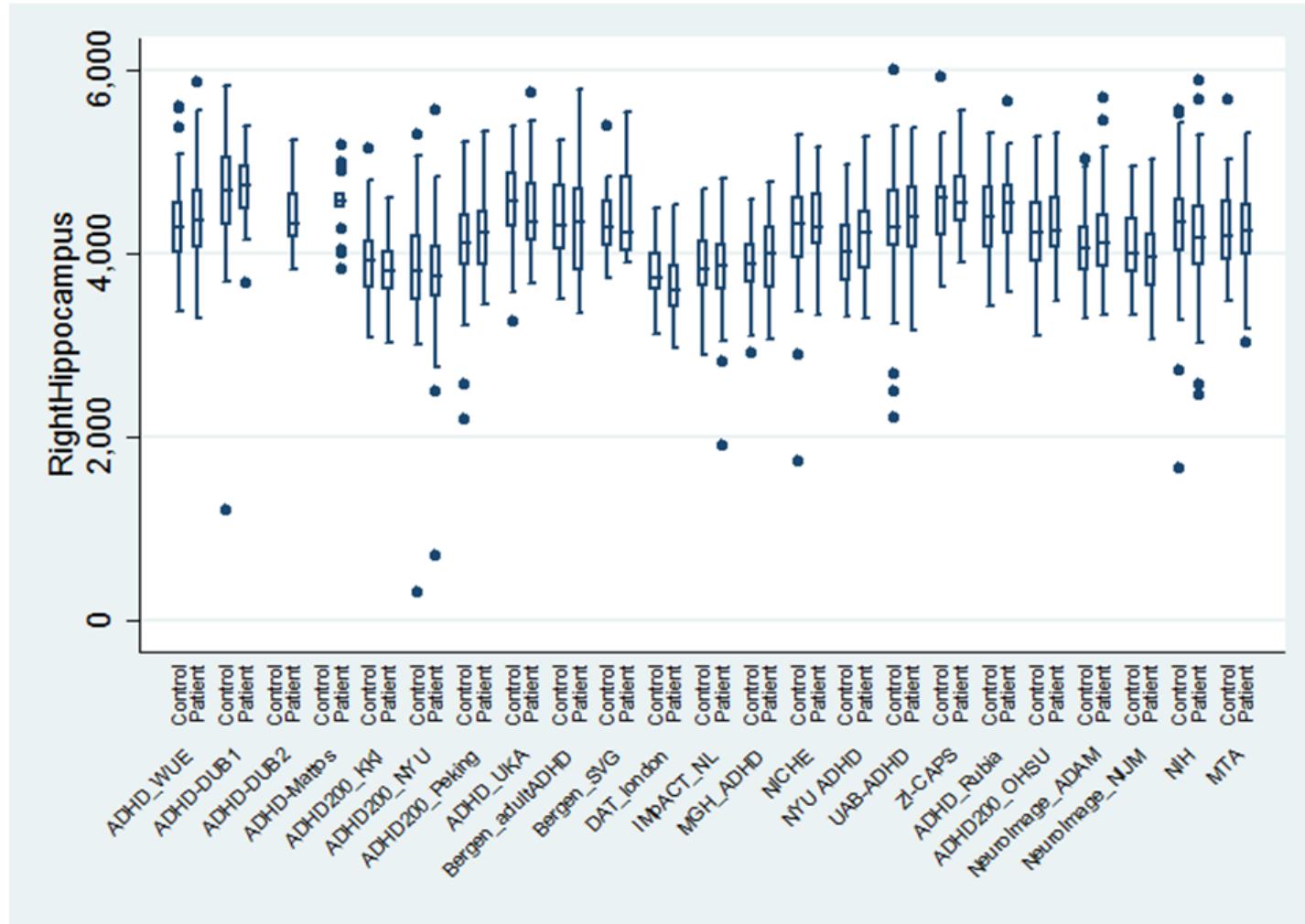
Boxplot for Right Caudate nucleus in mm<sup>3</sup> per sample, including outliers (>+/-1,5 IQR)



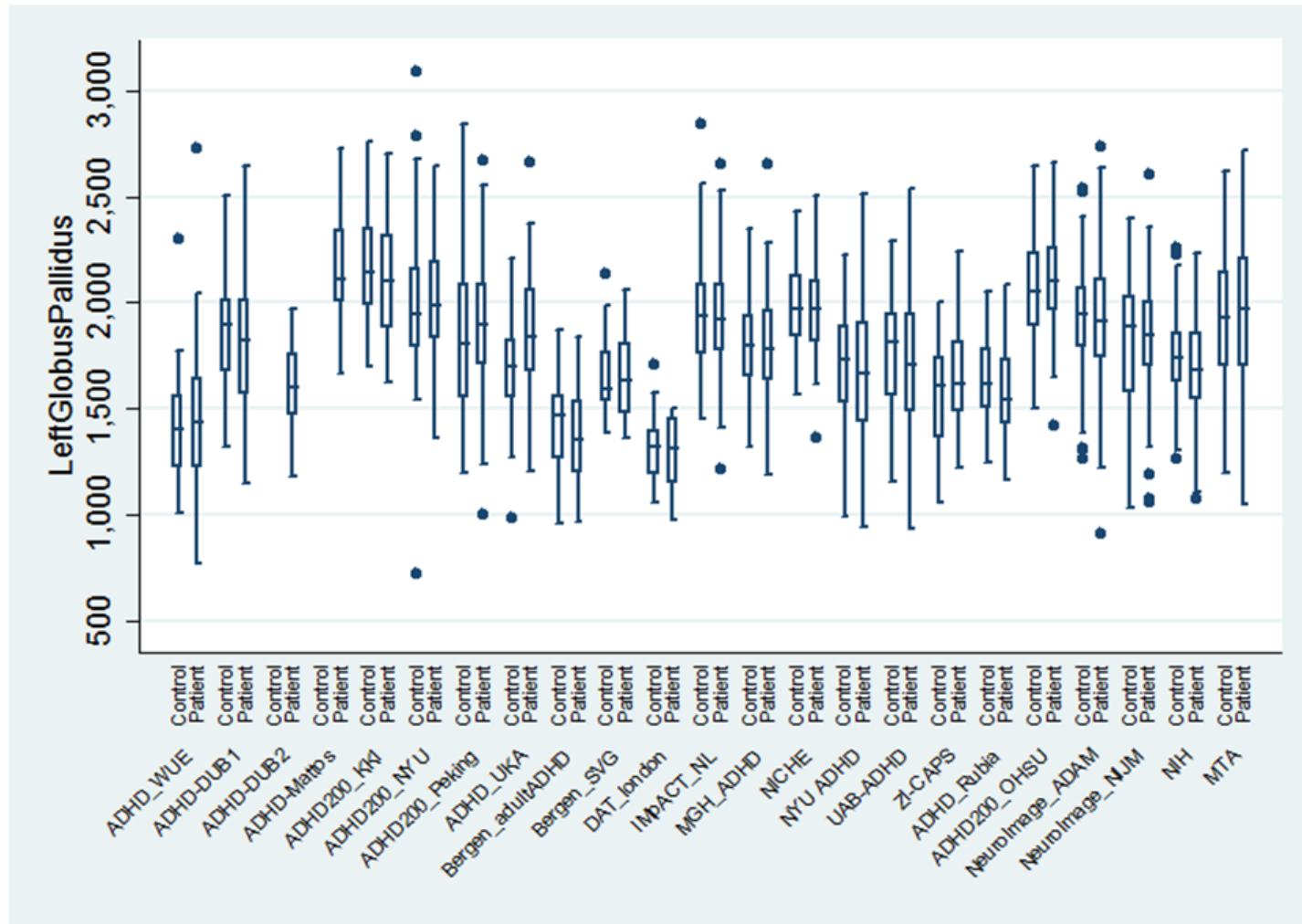
Boxplot for Left Hippocampus in mm<sup>3</sup> per sample, including outliers (>+/-1,5 IQR)



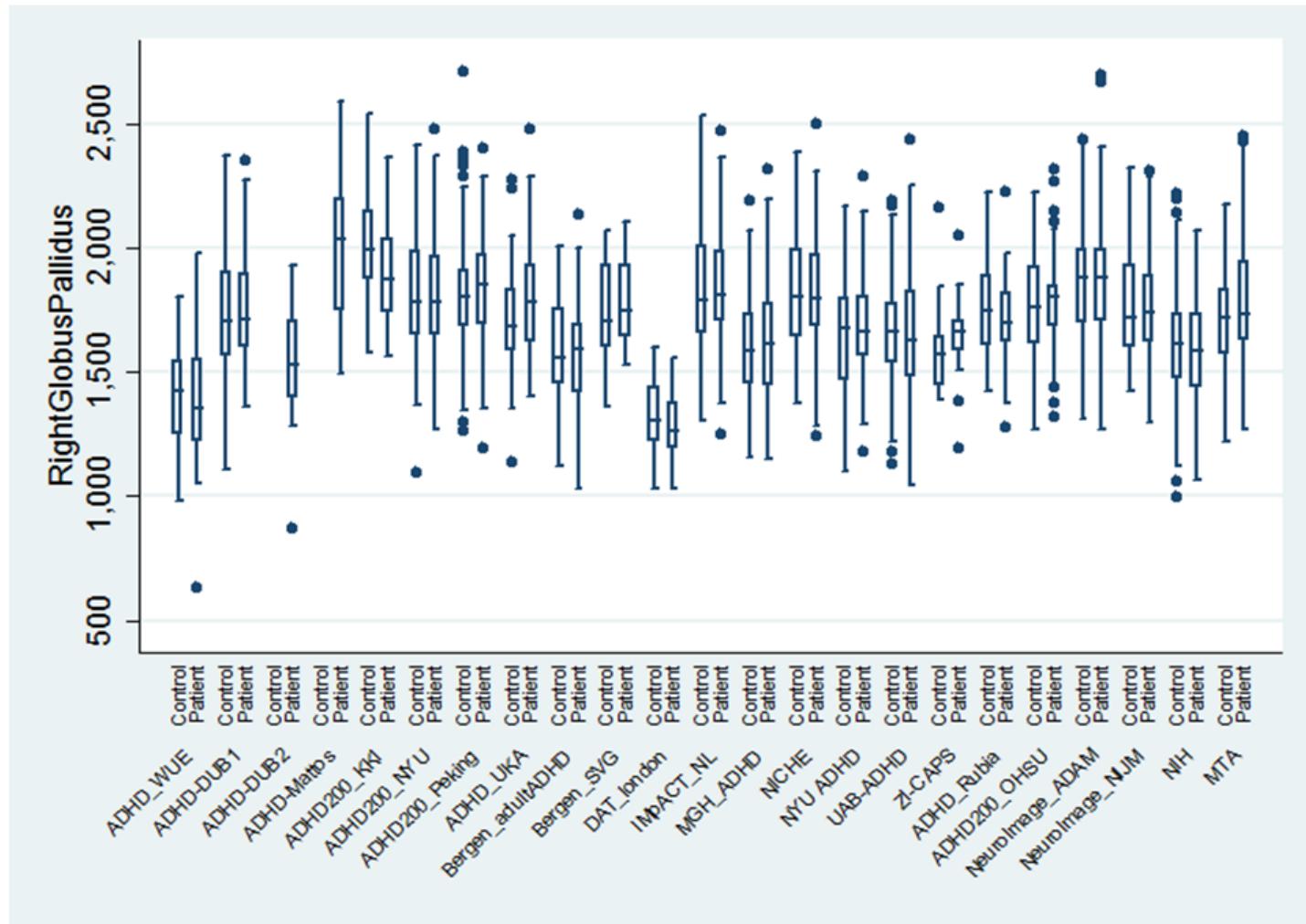
Boxplot for Right Hippocampus in mm<sup>3</sup> per sample, including outliers (>+/-1,5 IQR)



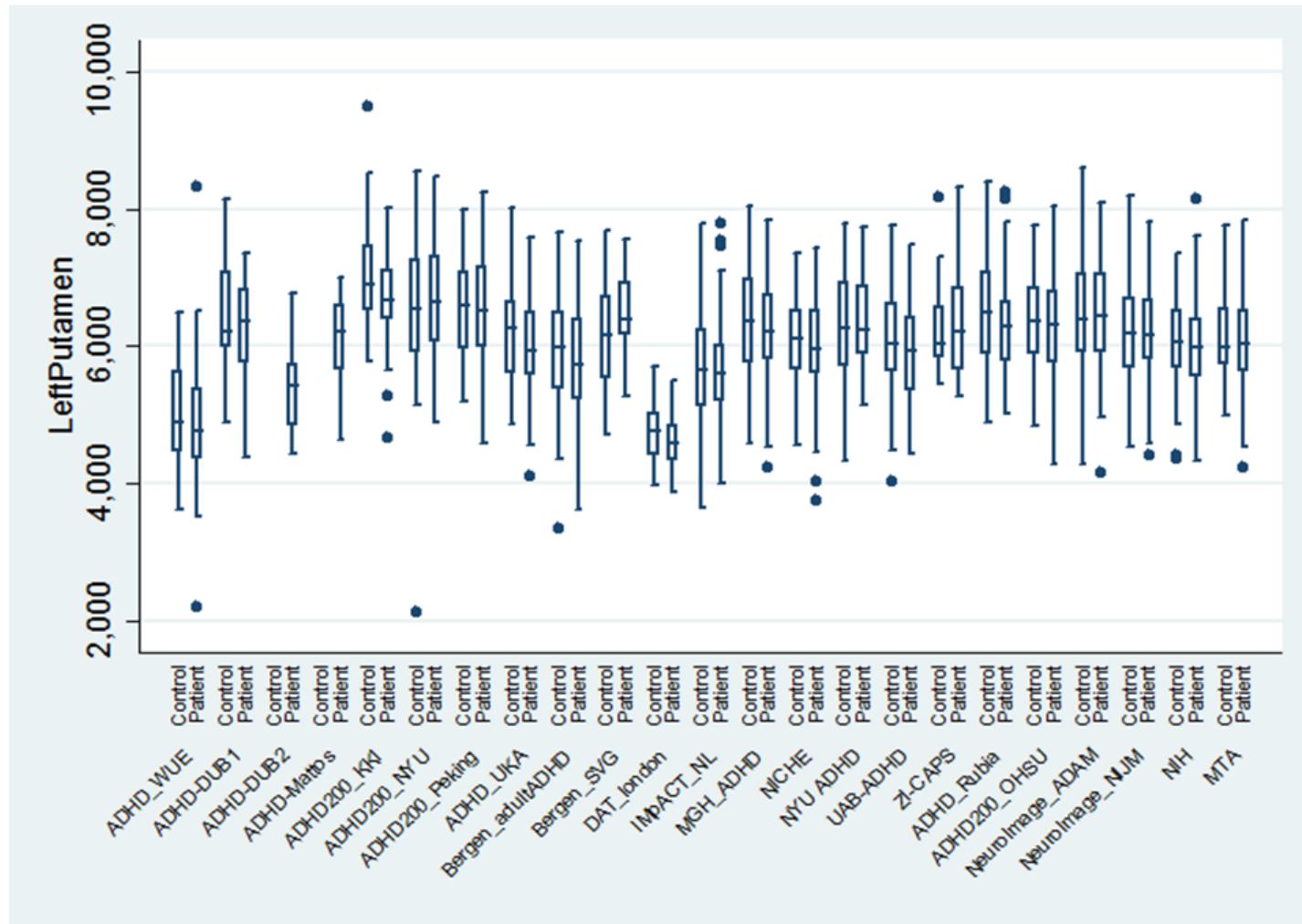
Boxplot for Left Globus Pallidum in mm<sup>3</sup> per sample, including outliers (>+/-1,5 IQR)



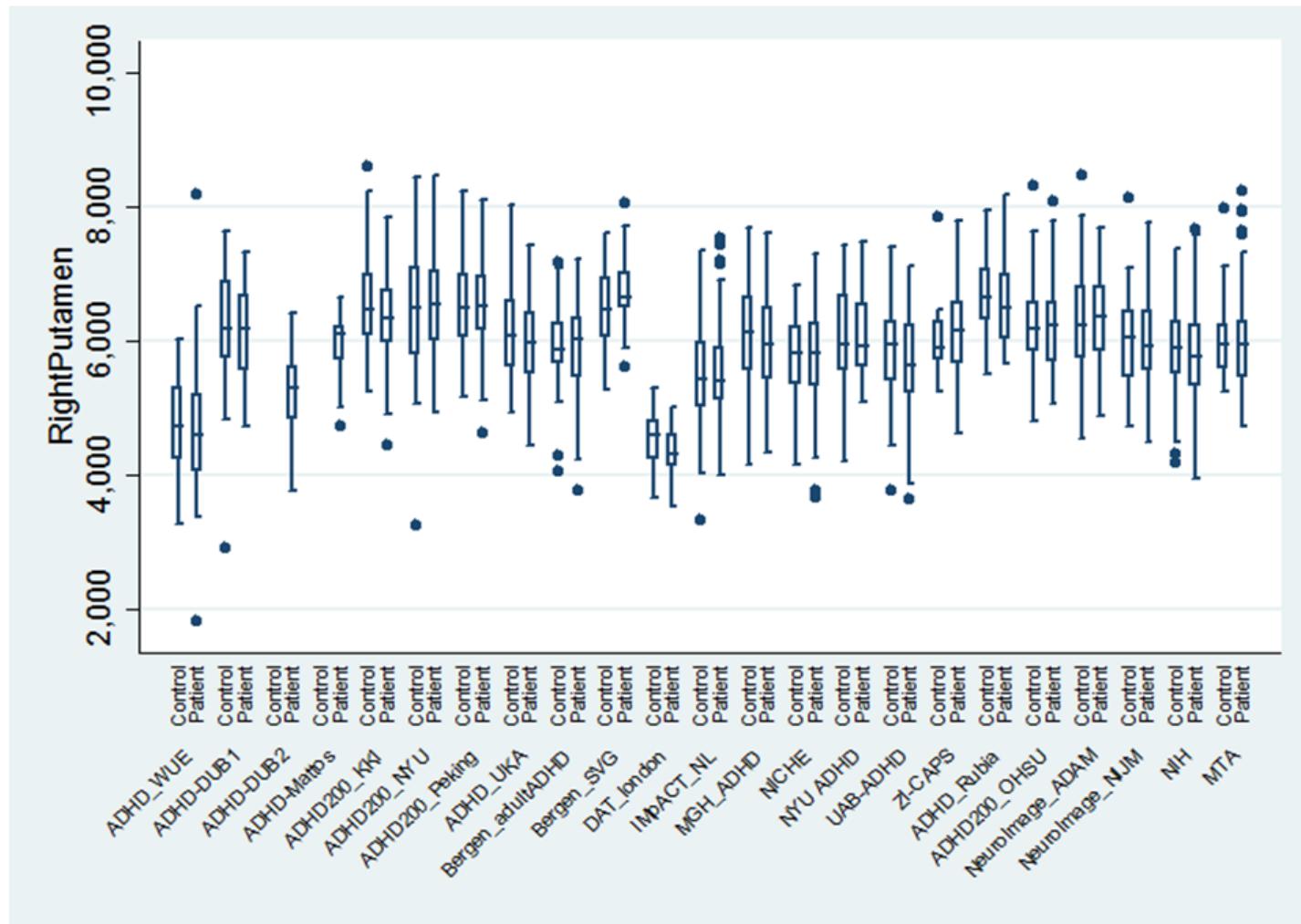
Boxplot for Right Pallidus in mm<sup>3</sup> per sample, including outliers (>+/-1,5 IQR)



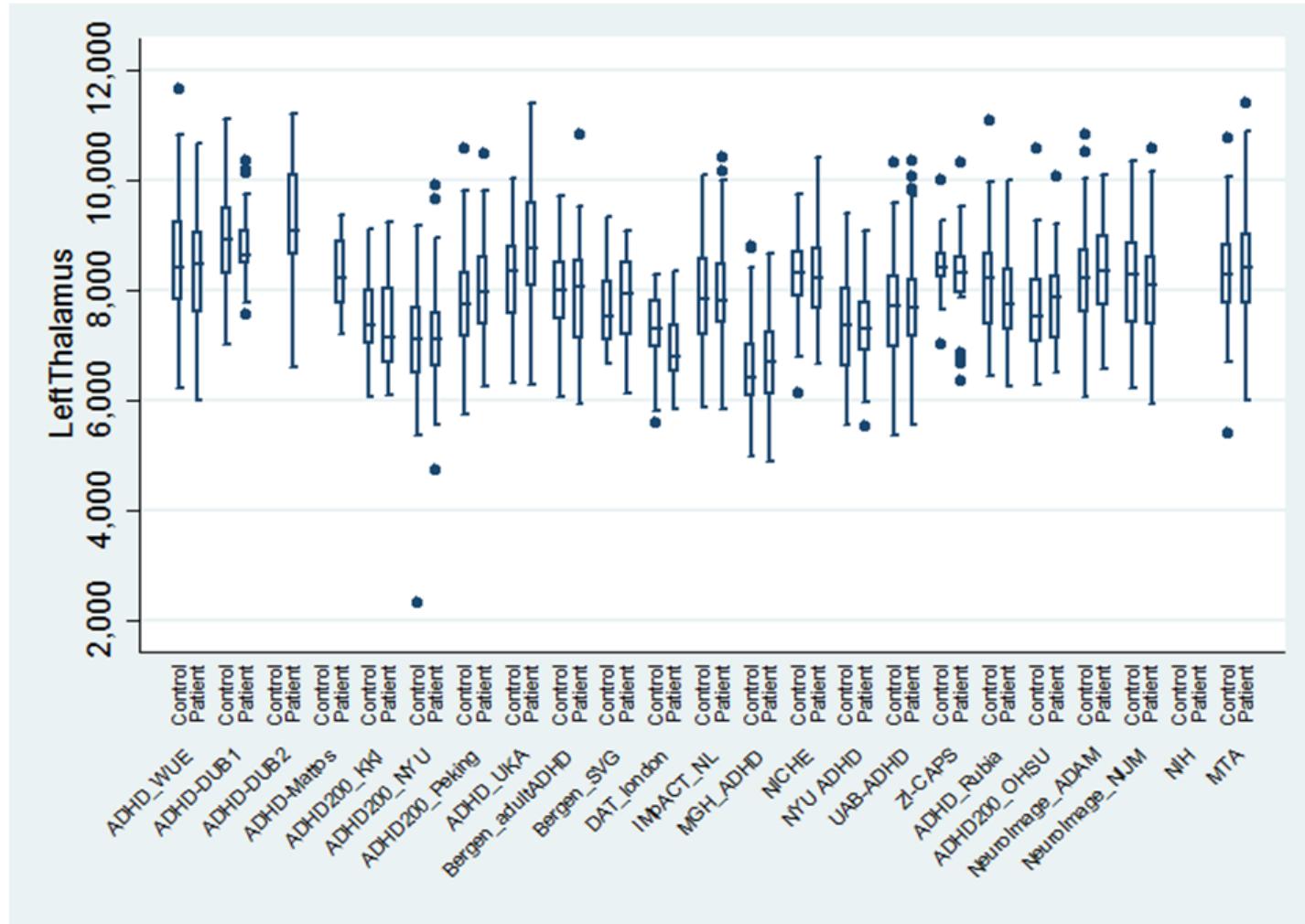
Boxplot for Left Putamen in mm<sup>3</sup> per sample, including outliers (>+/-1,5 IQR)



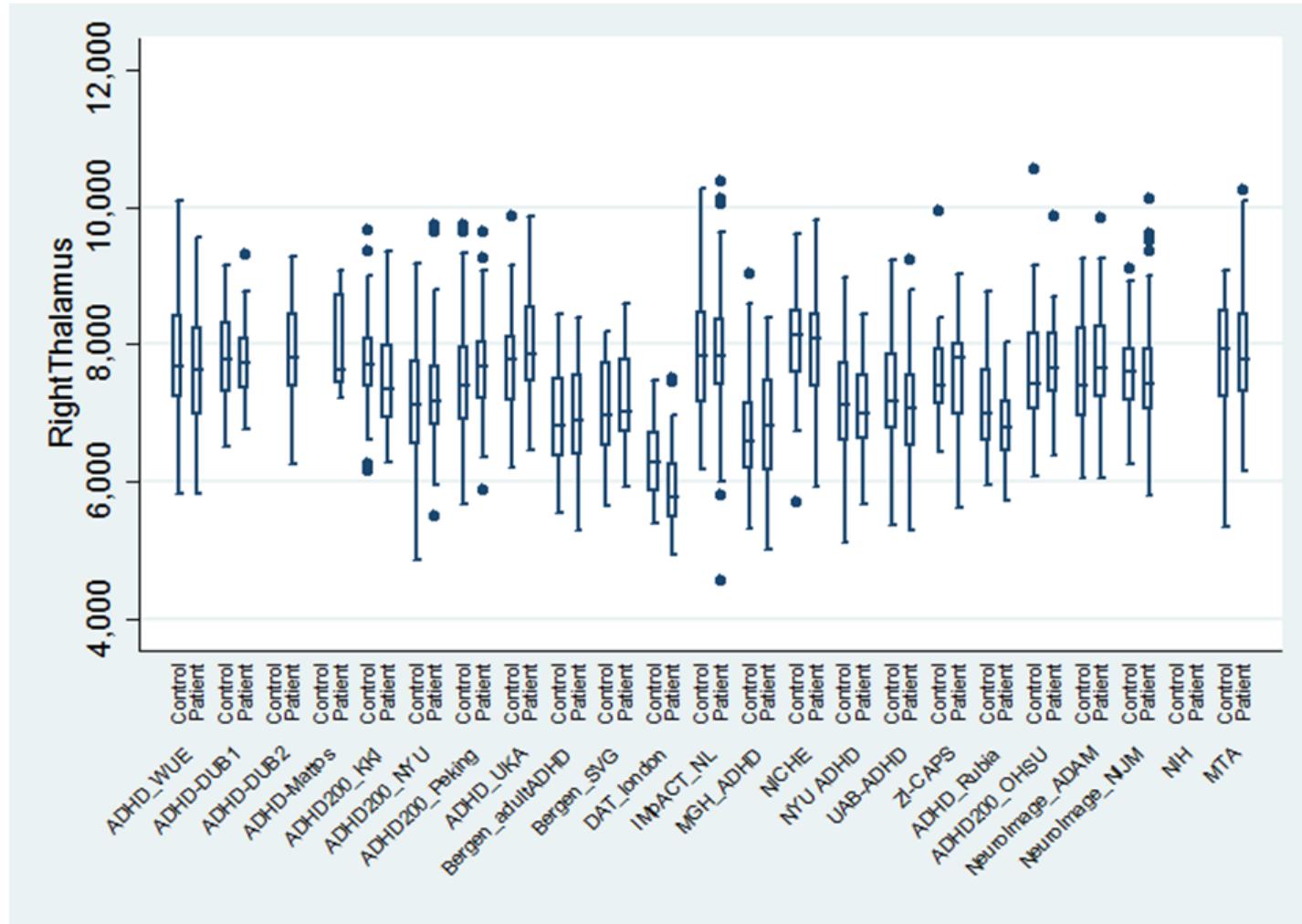
Boxplot for Right Putamen in mm<sup>3</sup> per sample, including outliers (>+/-1,5 IQR)



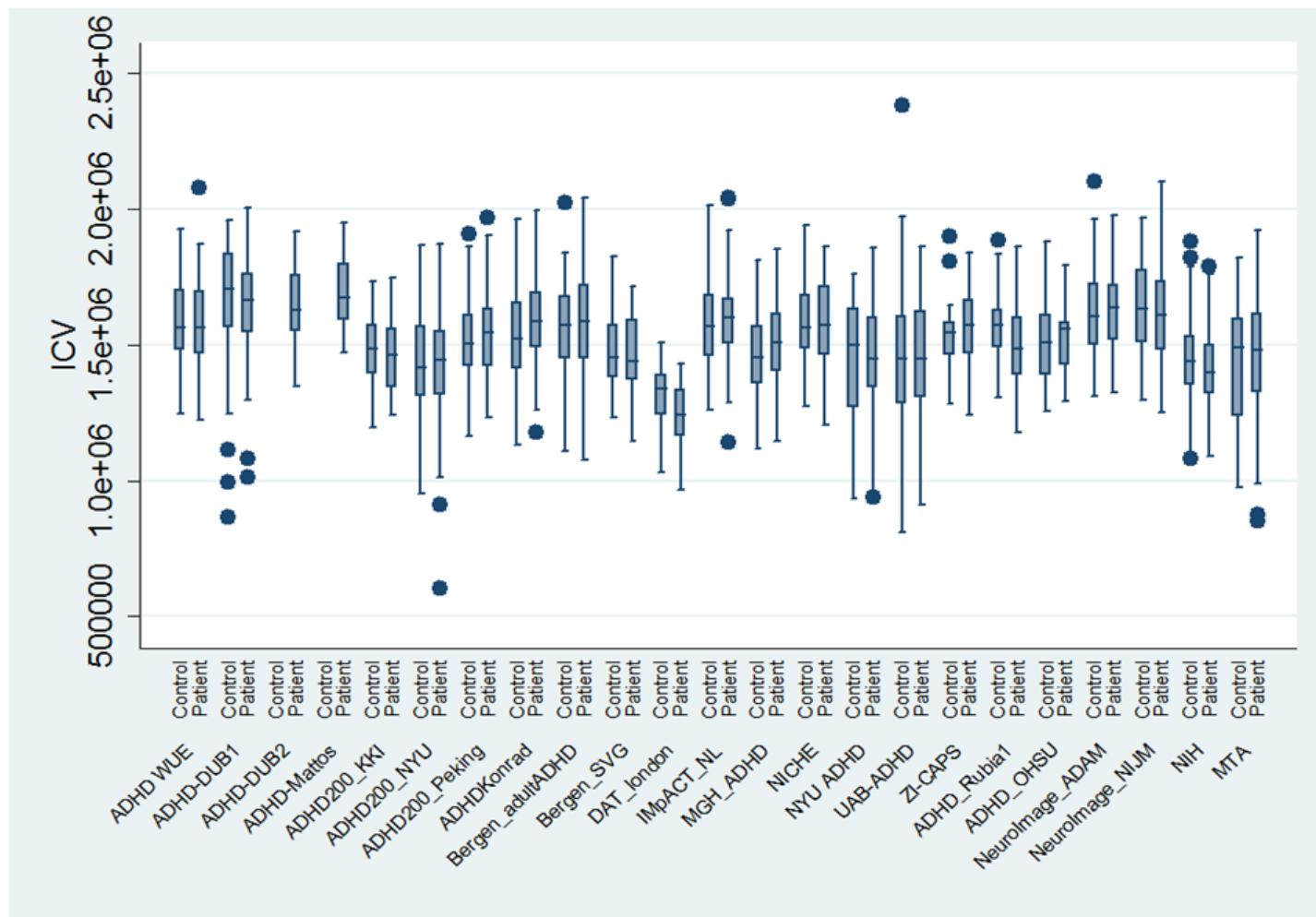
Boxplot for Left Thalamus in mm<sup>3</sup> per sample, including outliers (>+/-1,5 IQR)



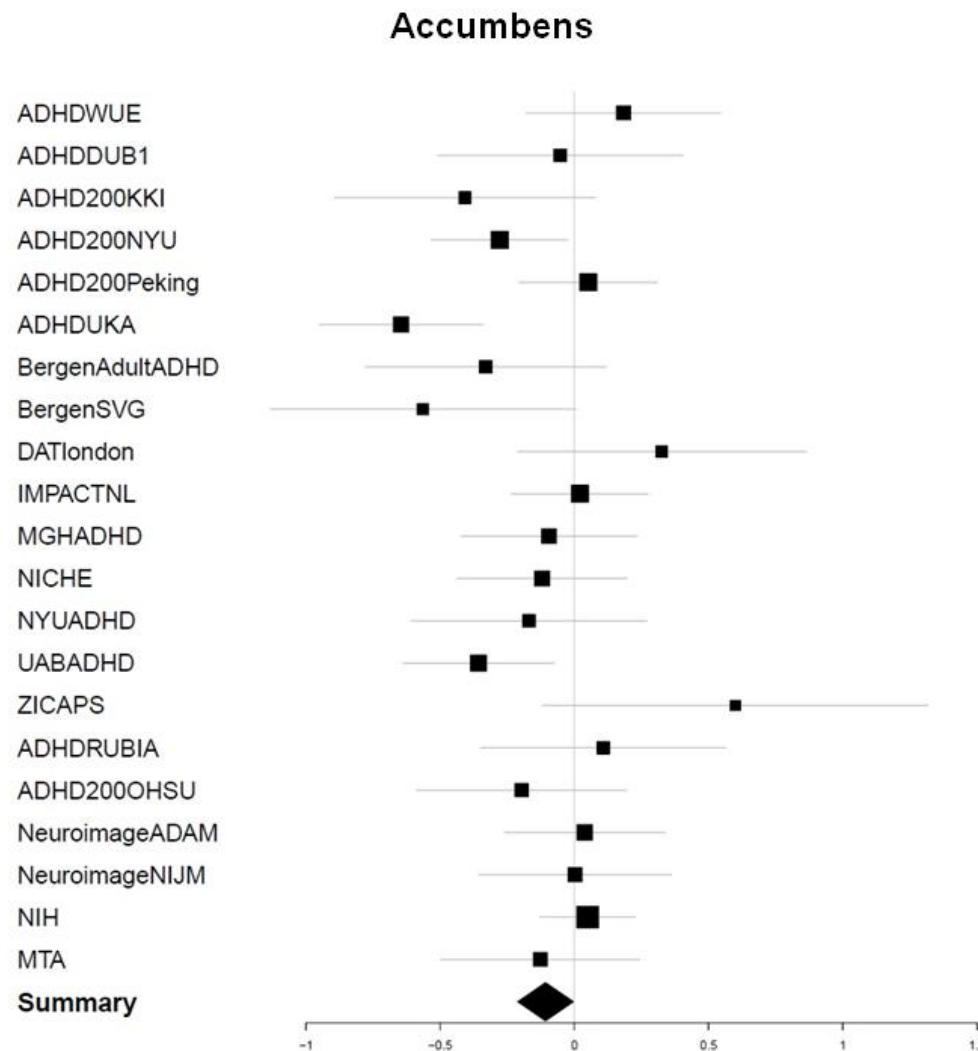
Boxplot for Right Thalamus in mm<sup>3</sup> per sample, including outliers (>+/-1,5 IQR)



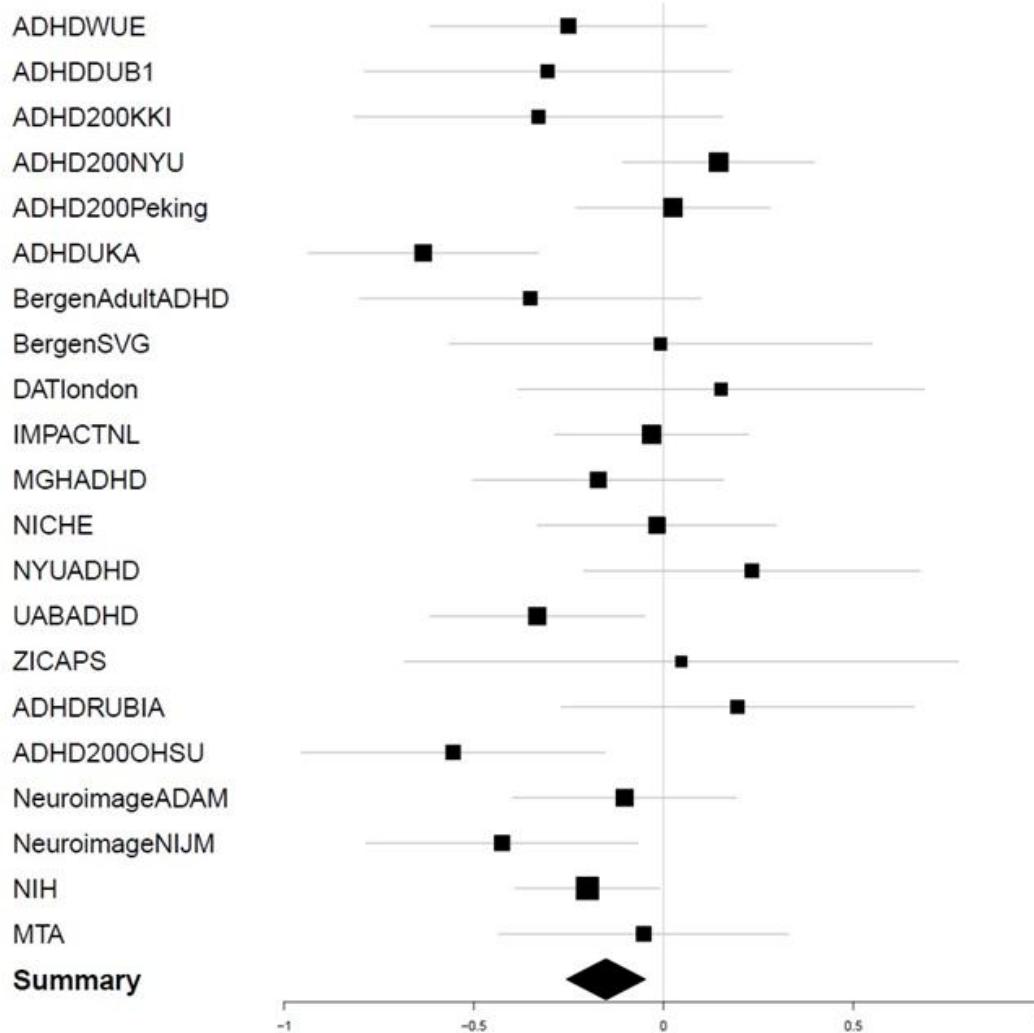
Boxplot for ICV in mm<sup>3</sup> per sample, including outliers (>+/-1,5 IQR)



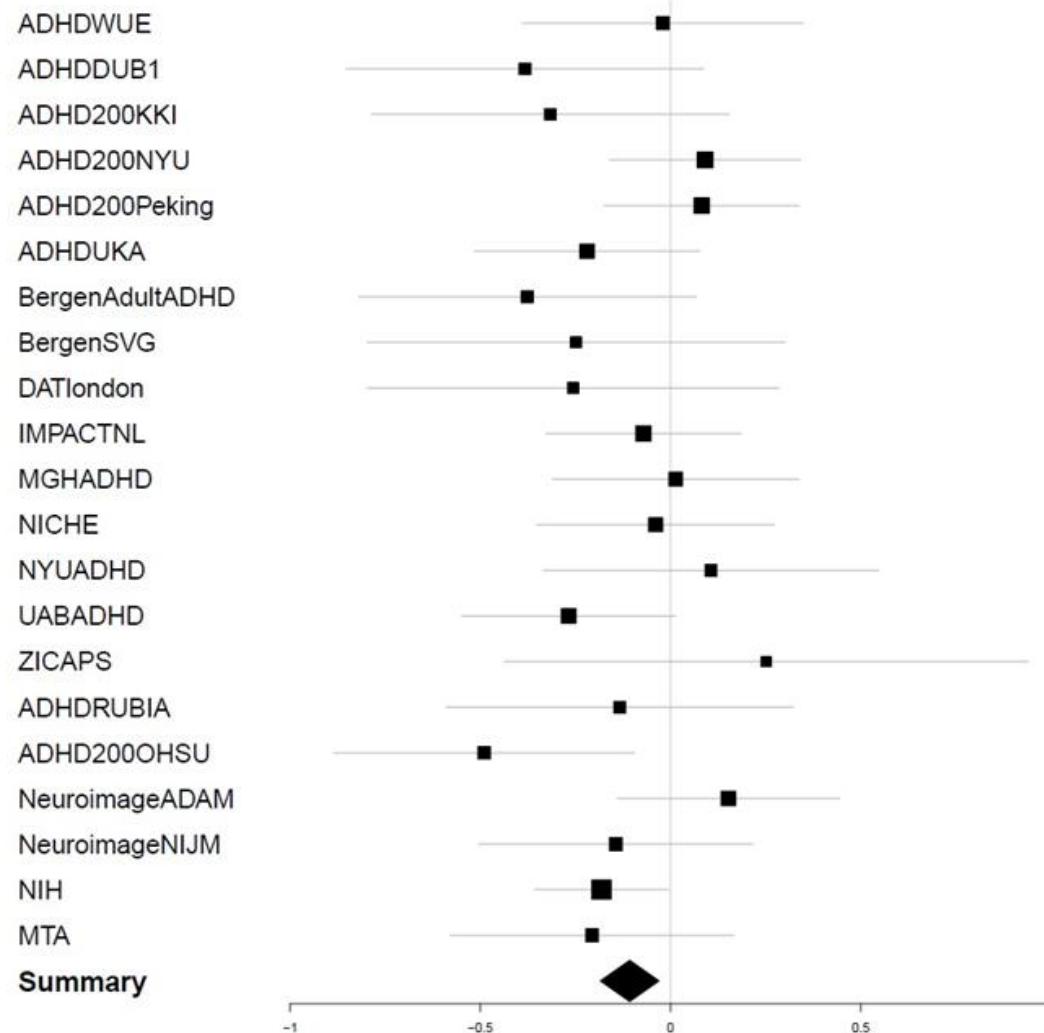
**sFigure2.** Forest plots: results of the meta-analysis of case-control differences in subcortical brain volume.



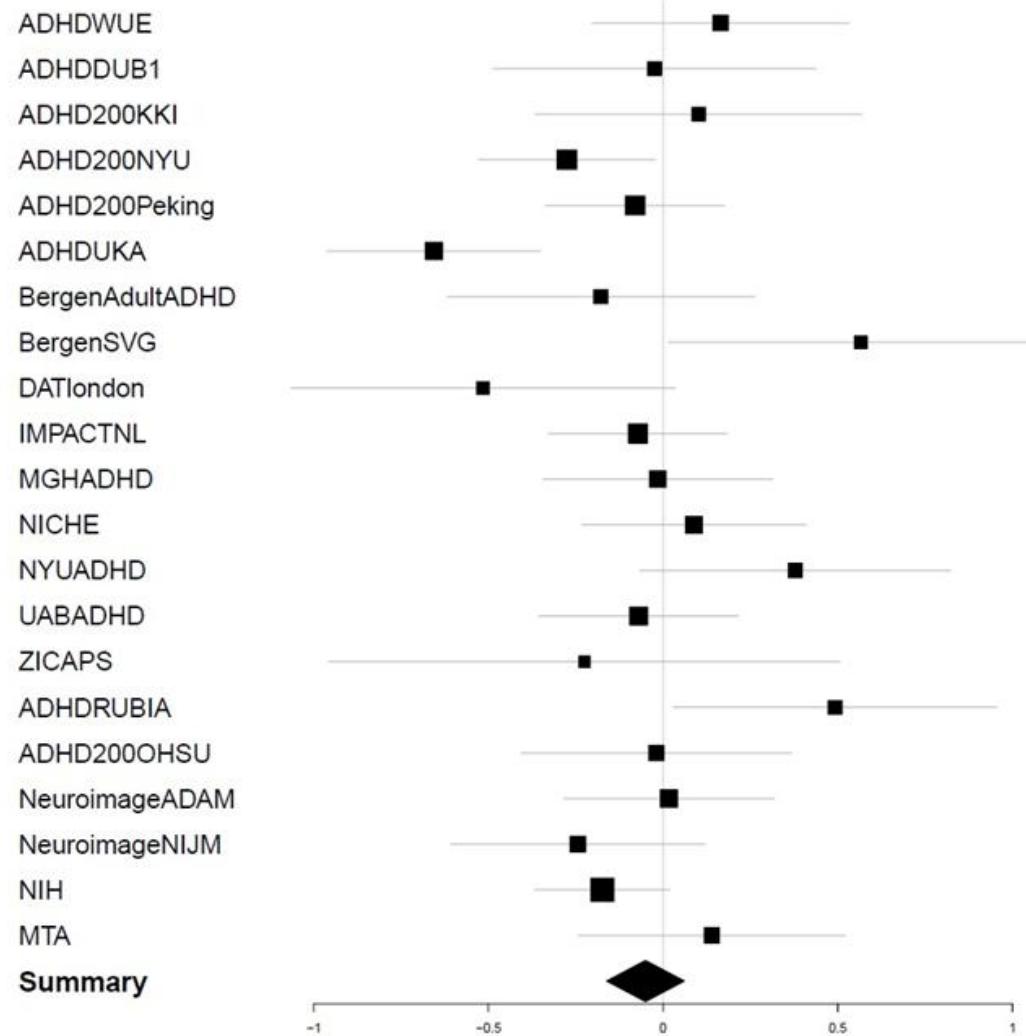
## Amygdala



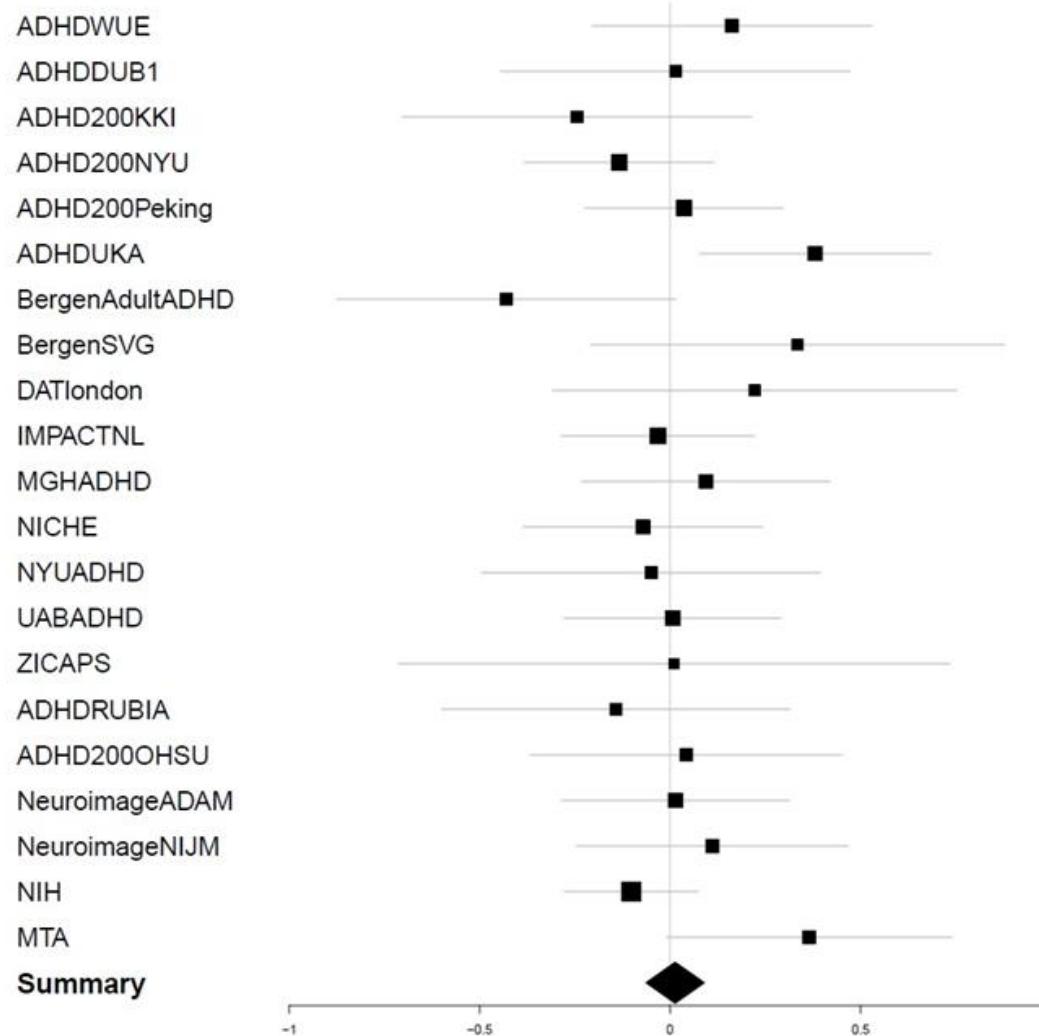
## Caudate



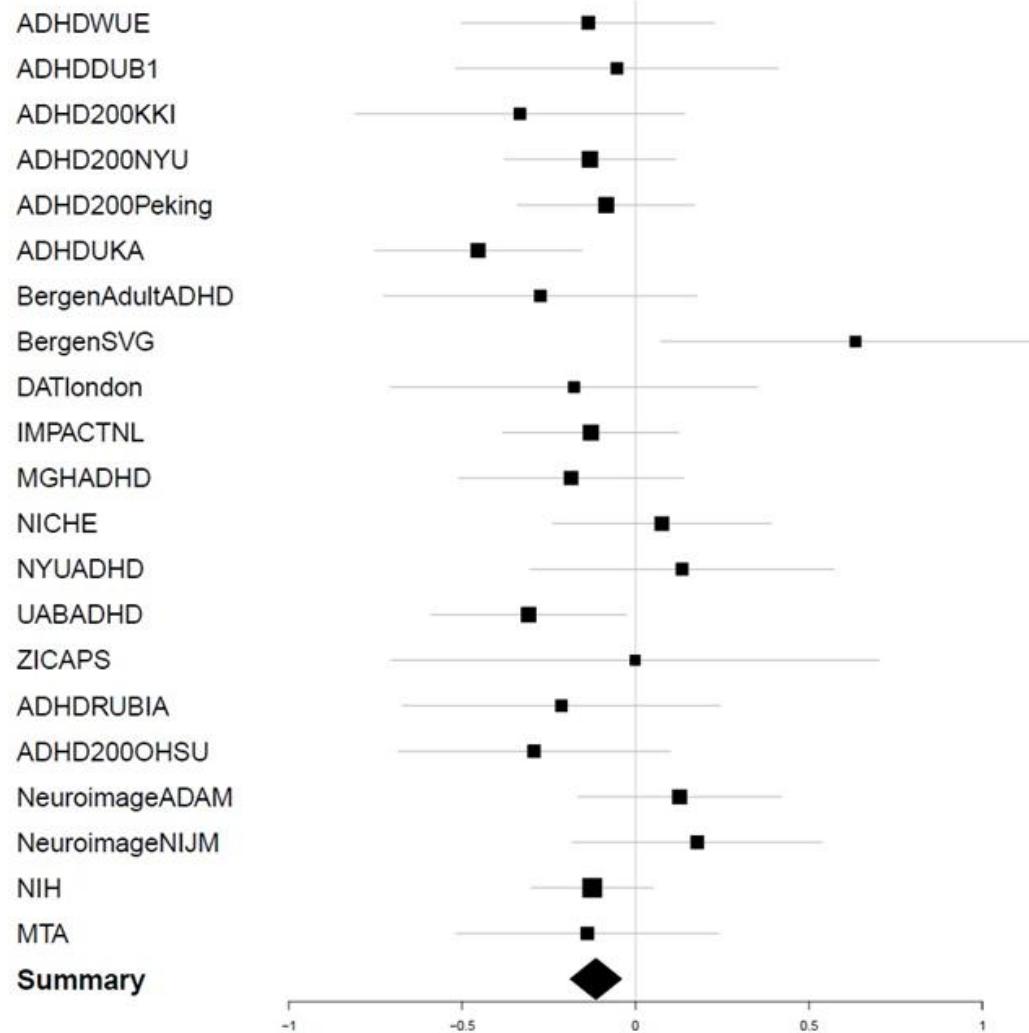
## Hippocampus



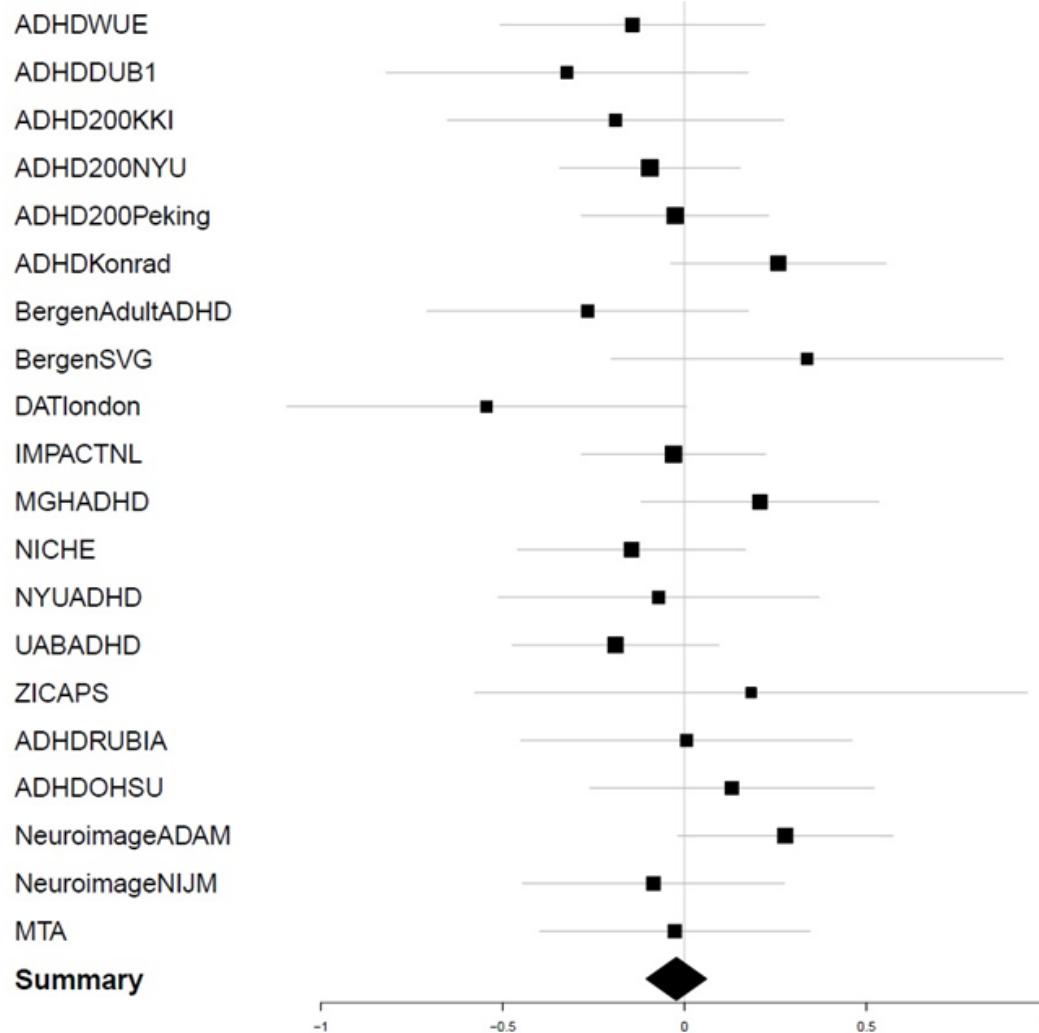
## Pallidum



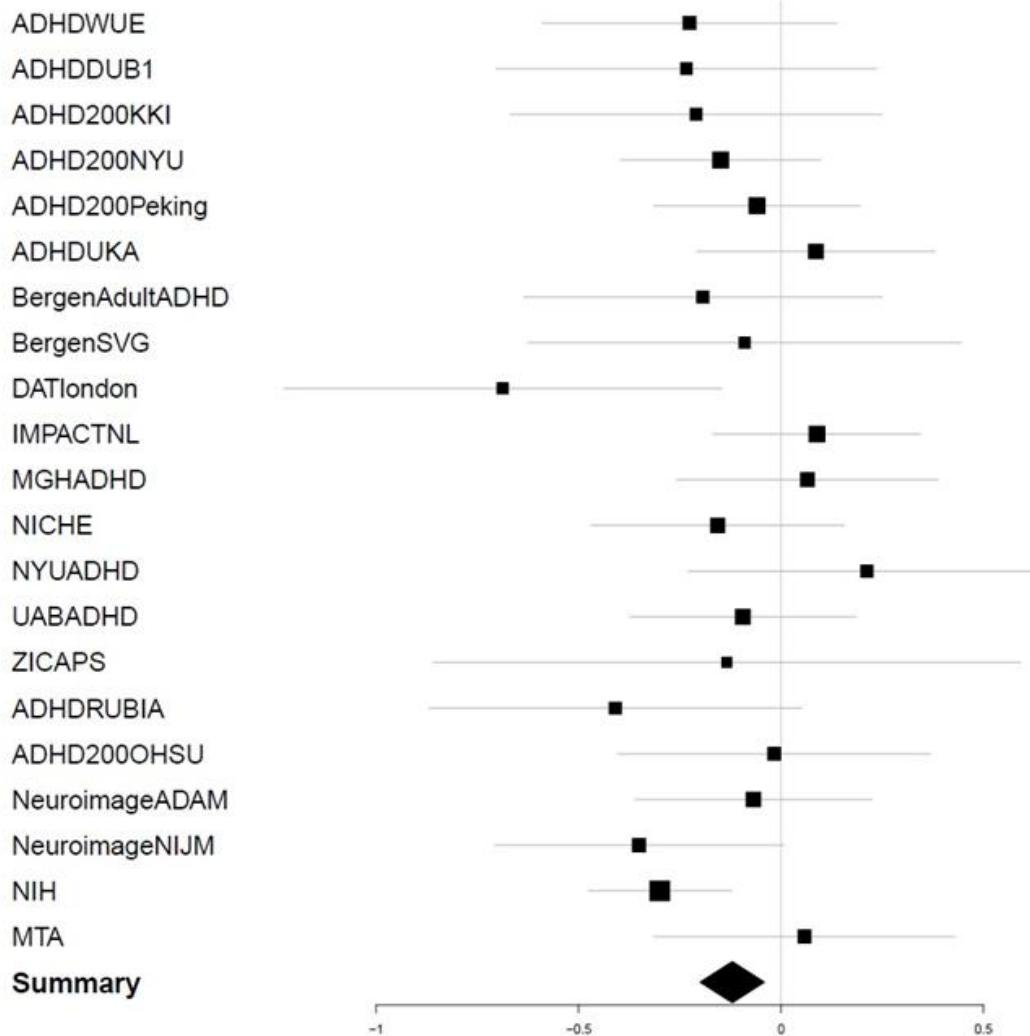
## Putamen



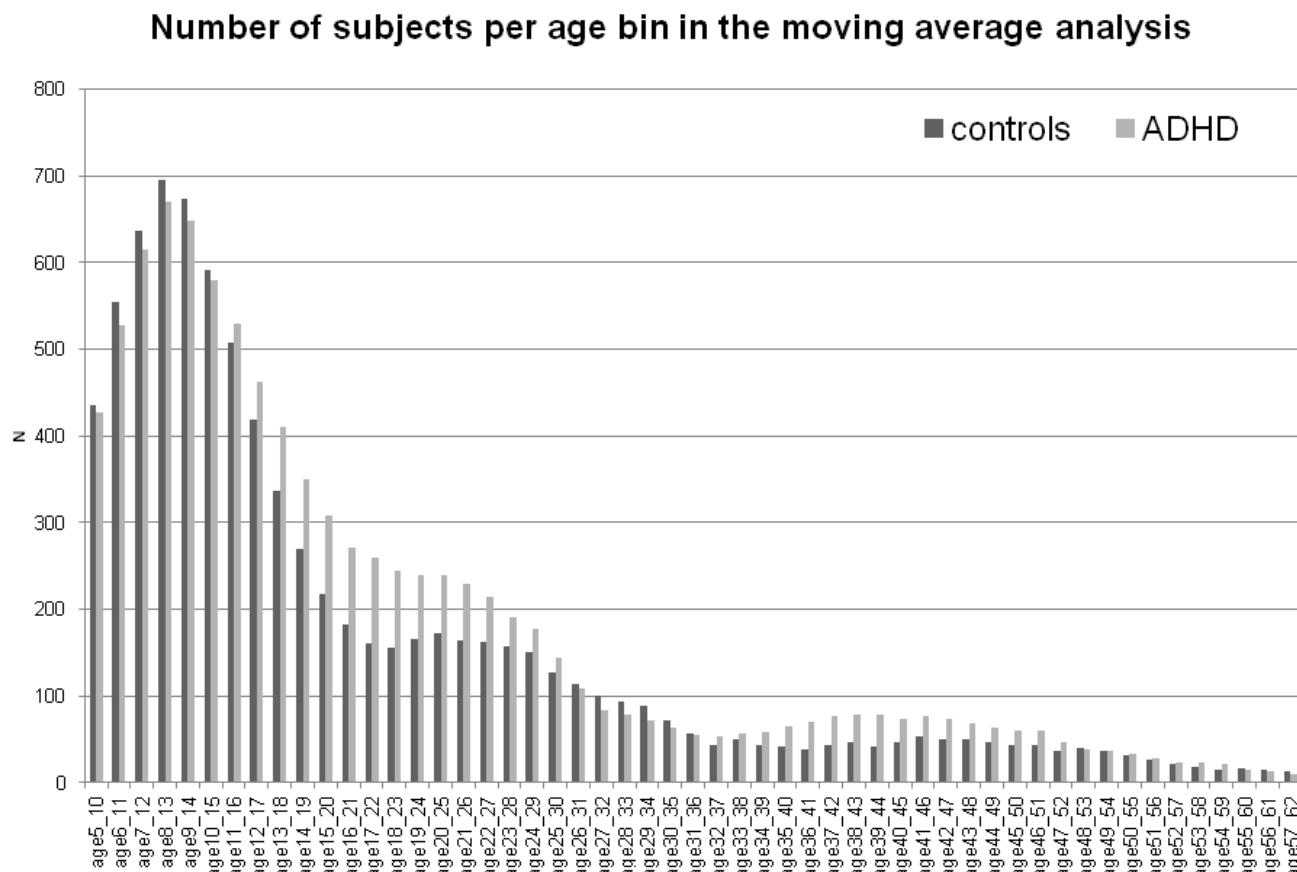
## Thalamus



## ICV

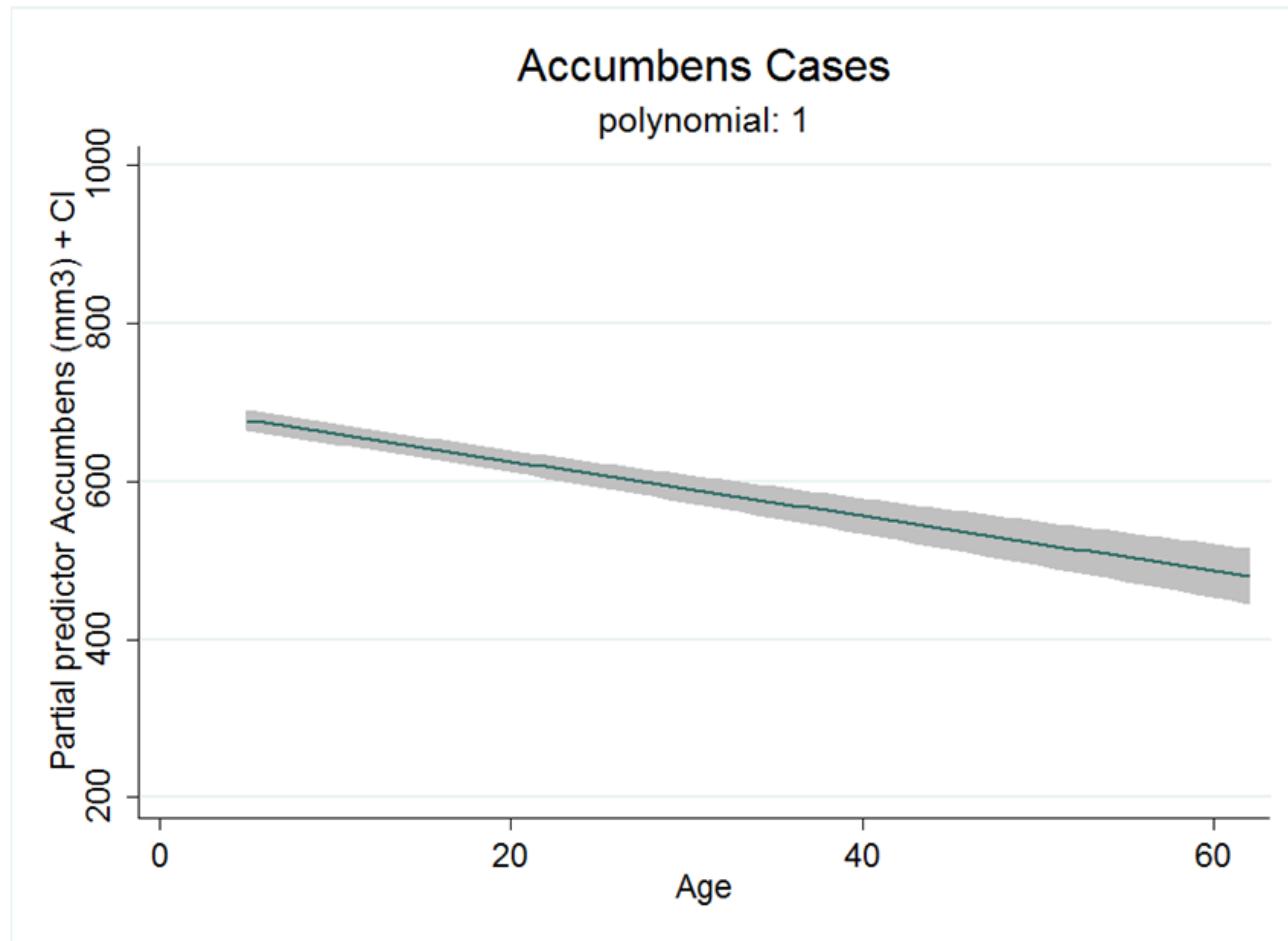


**sFigure3.** Number of subjects per age bin.



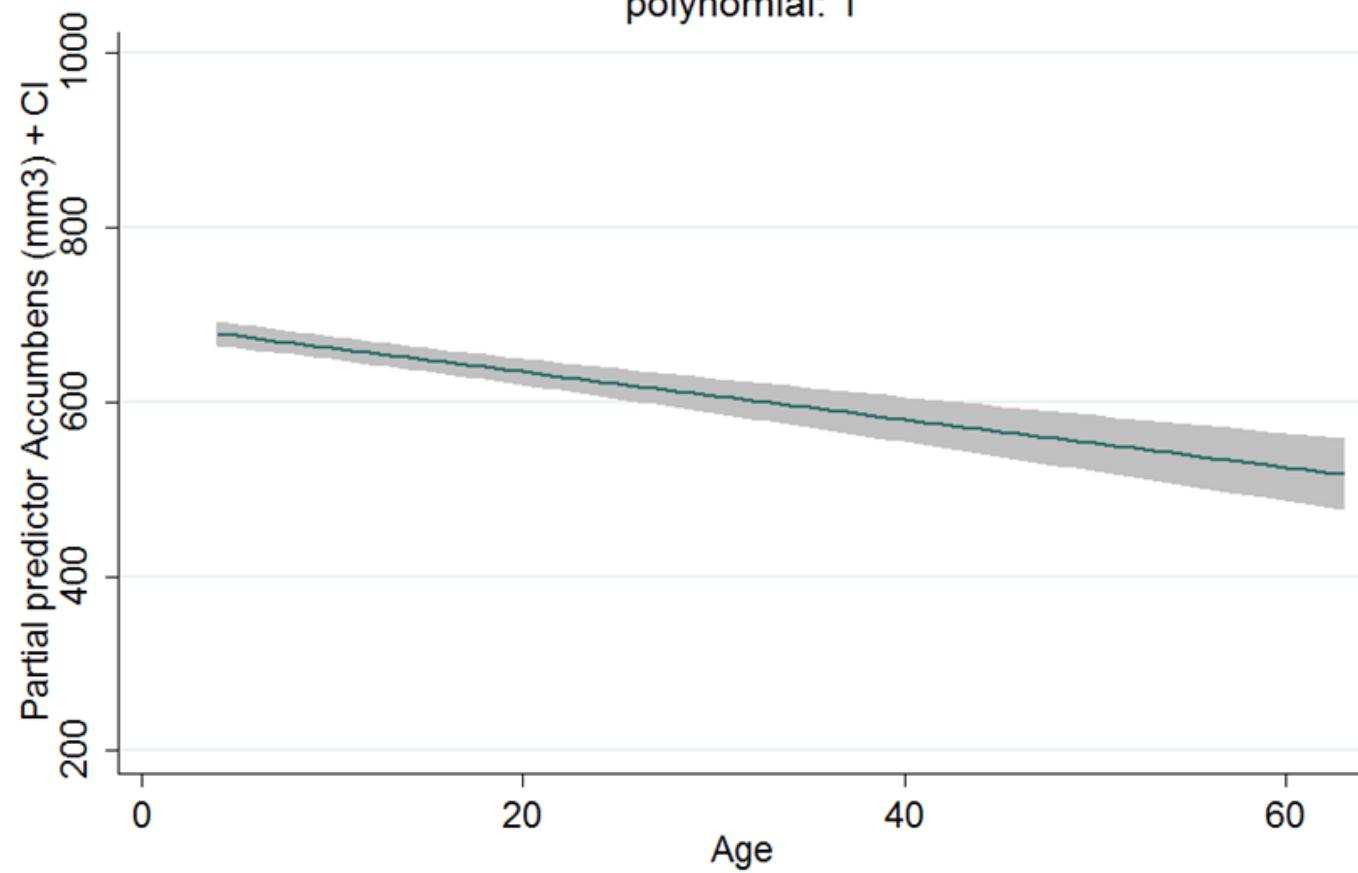
Displayed are the sample sizes per age bin for healthy controls and for participants with ADHD.

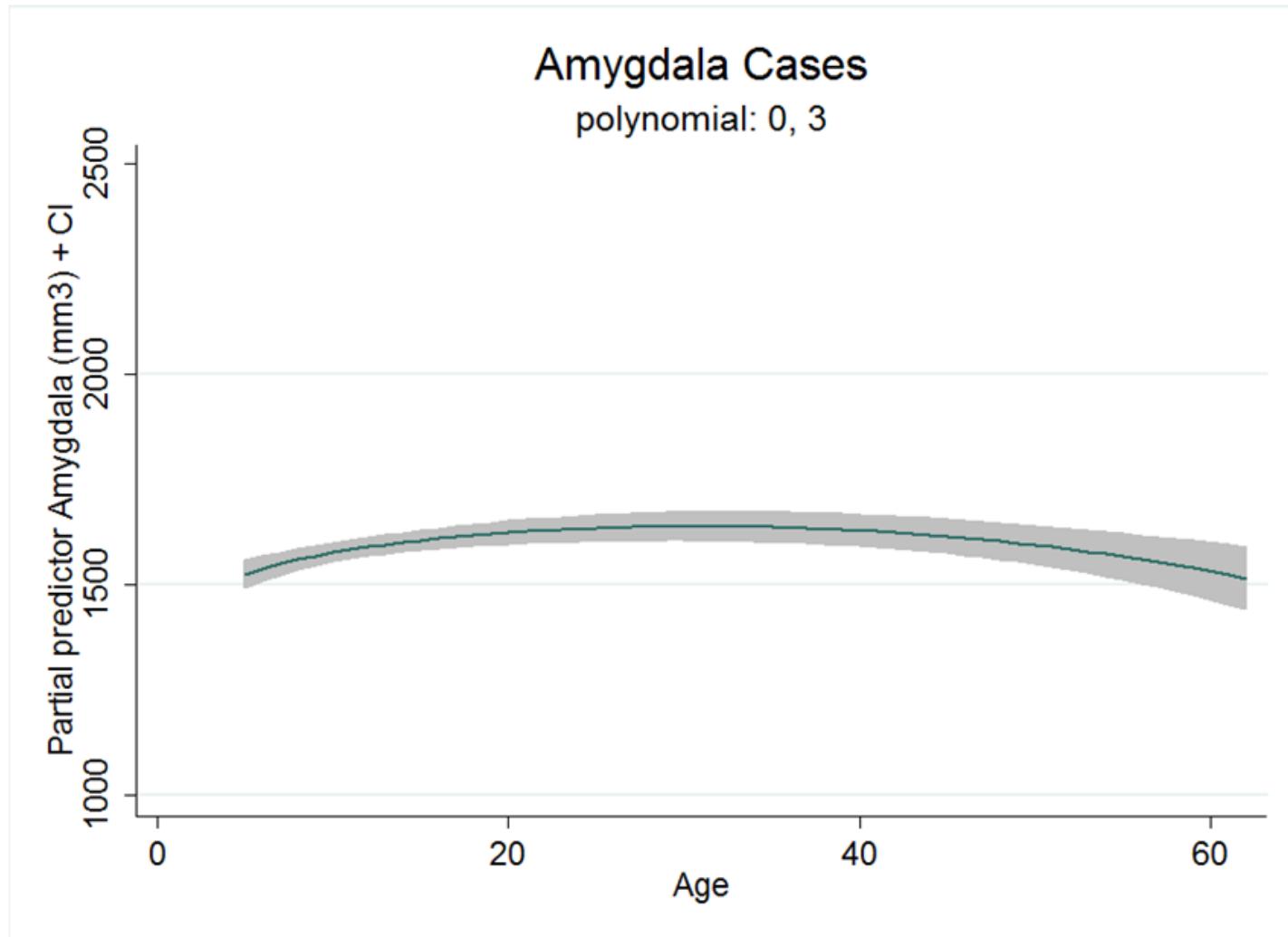
**sFigure4.** Results of the fractional polynomial analysis for the subcortical brain volumes.

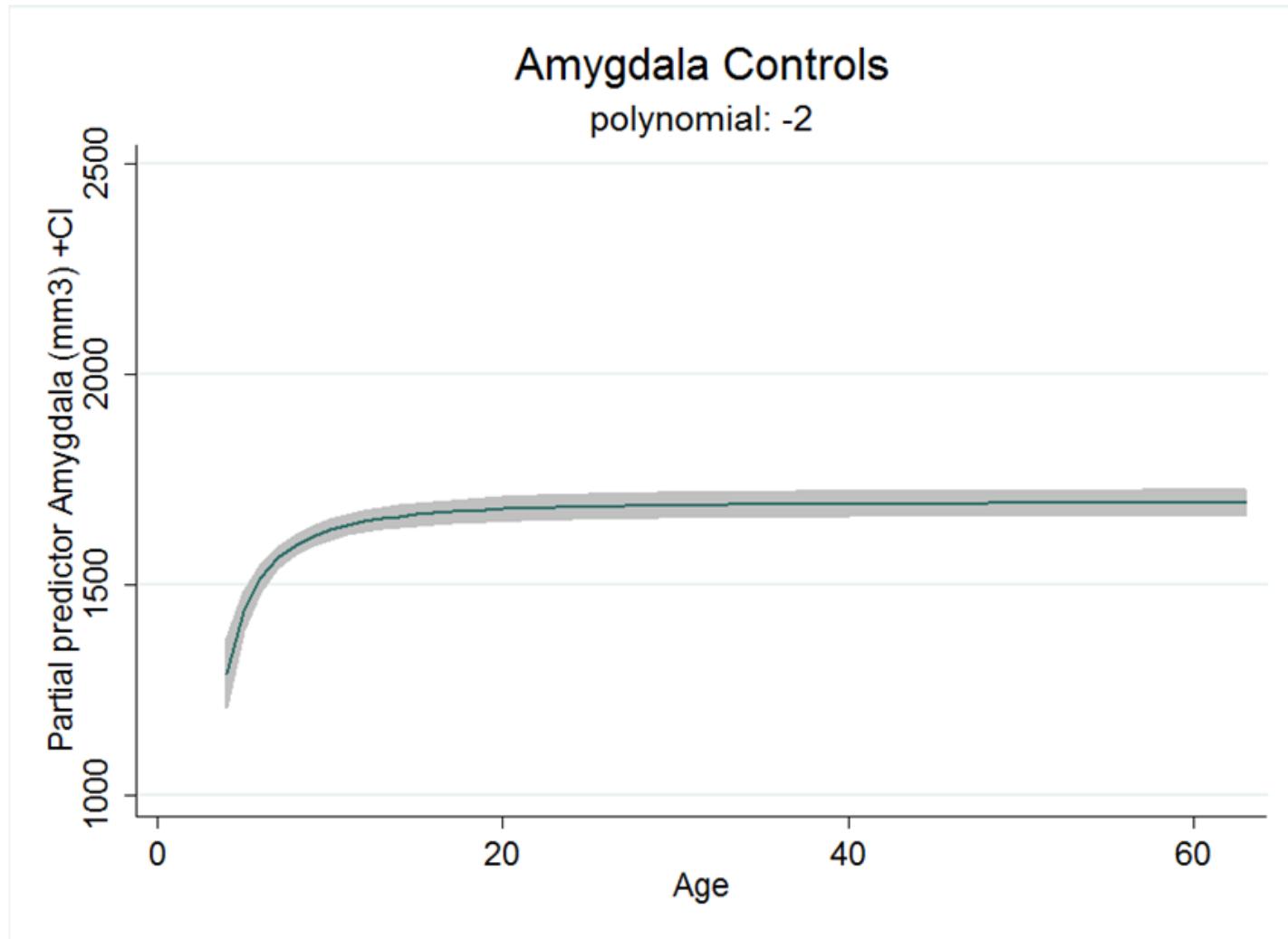


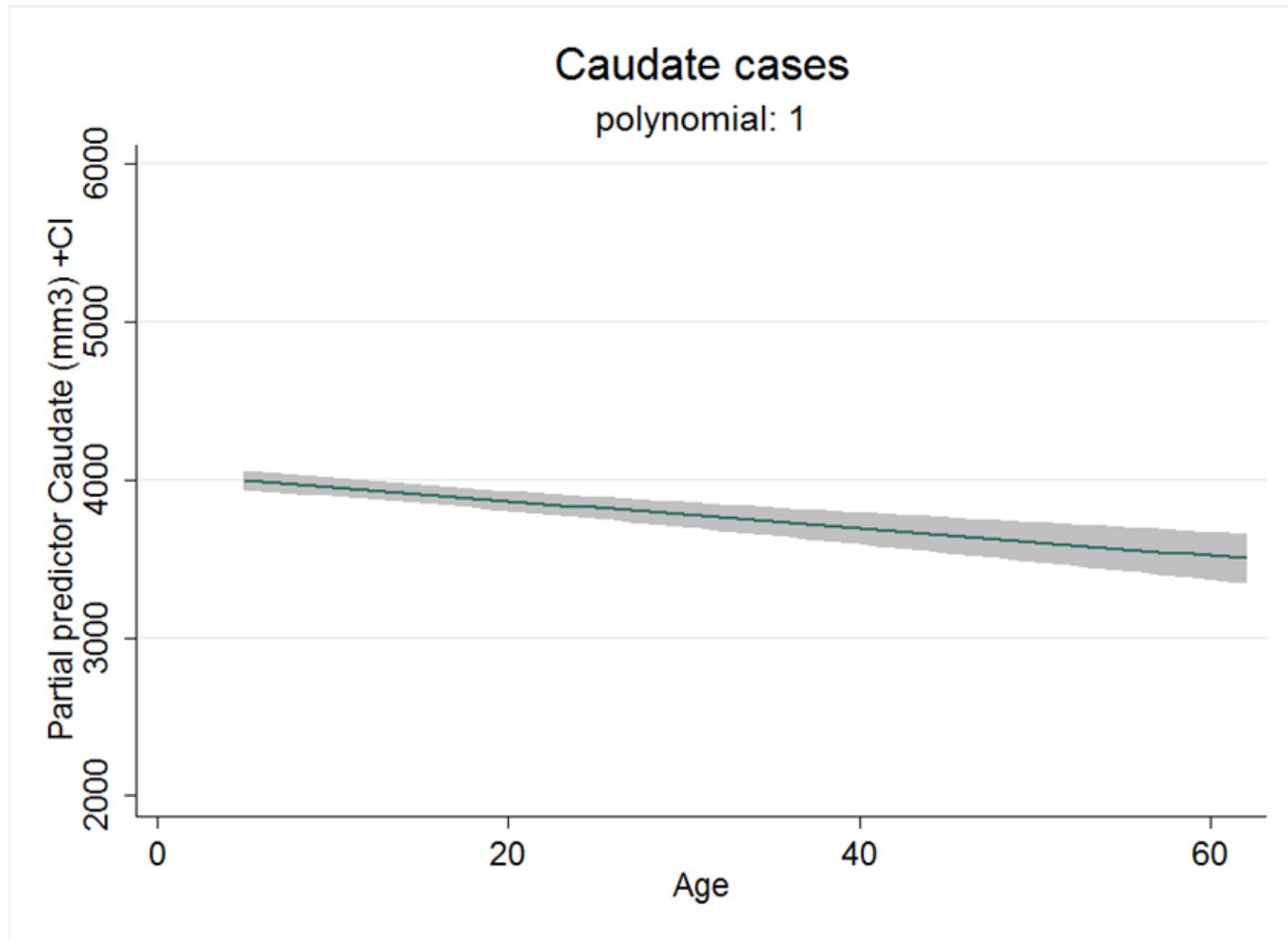
## Accumbens Controls

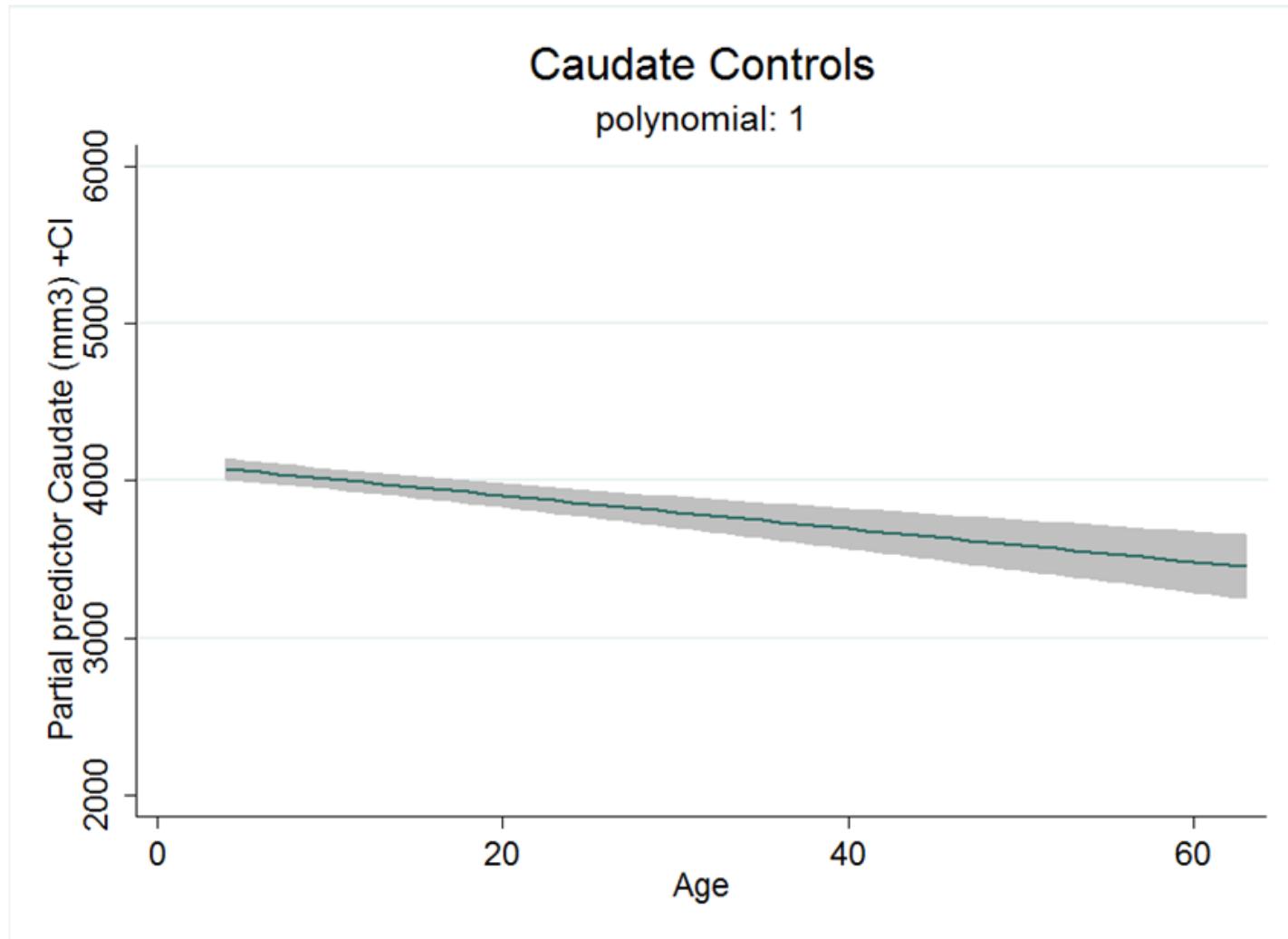
polynomial: 1





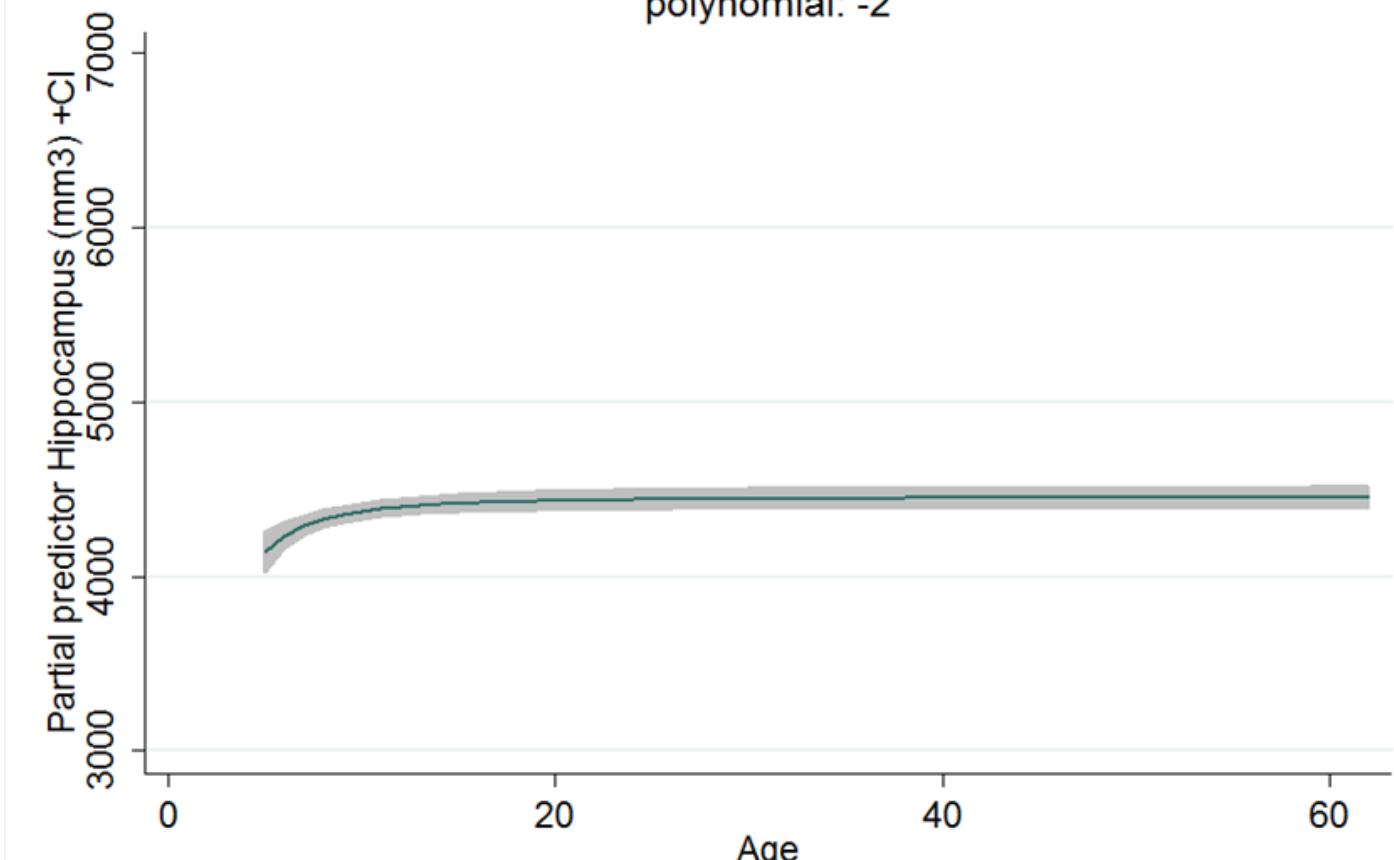






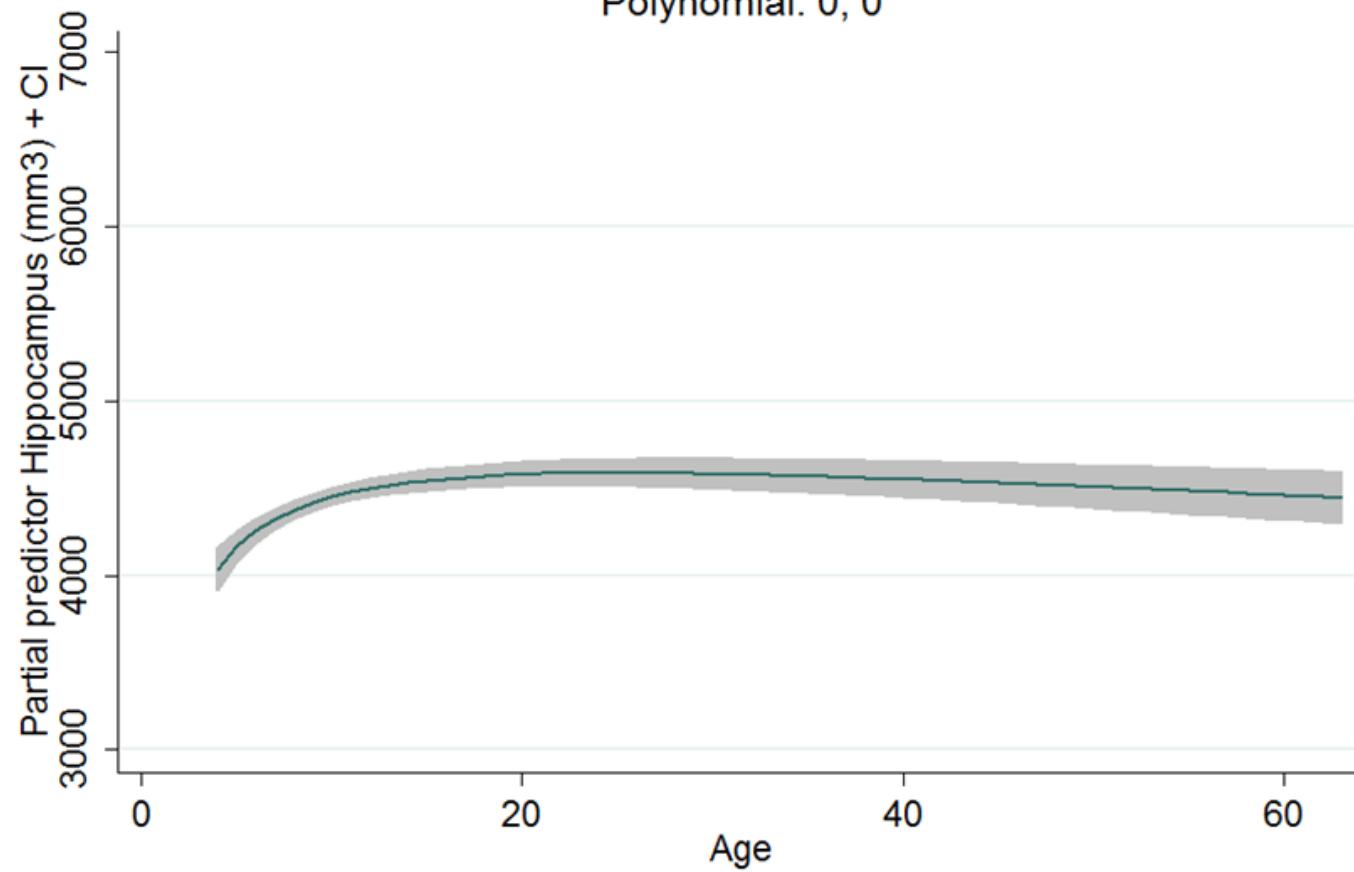
## Hippocampus Cases

polynomial: -2



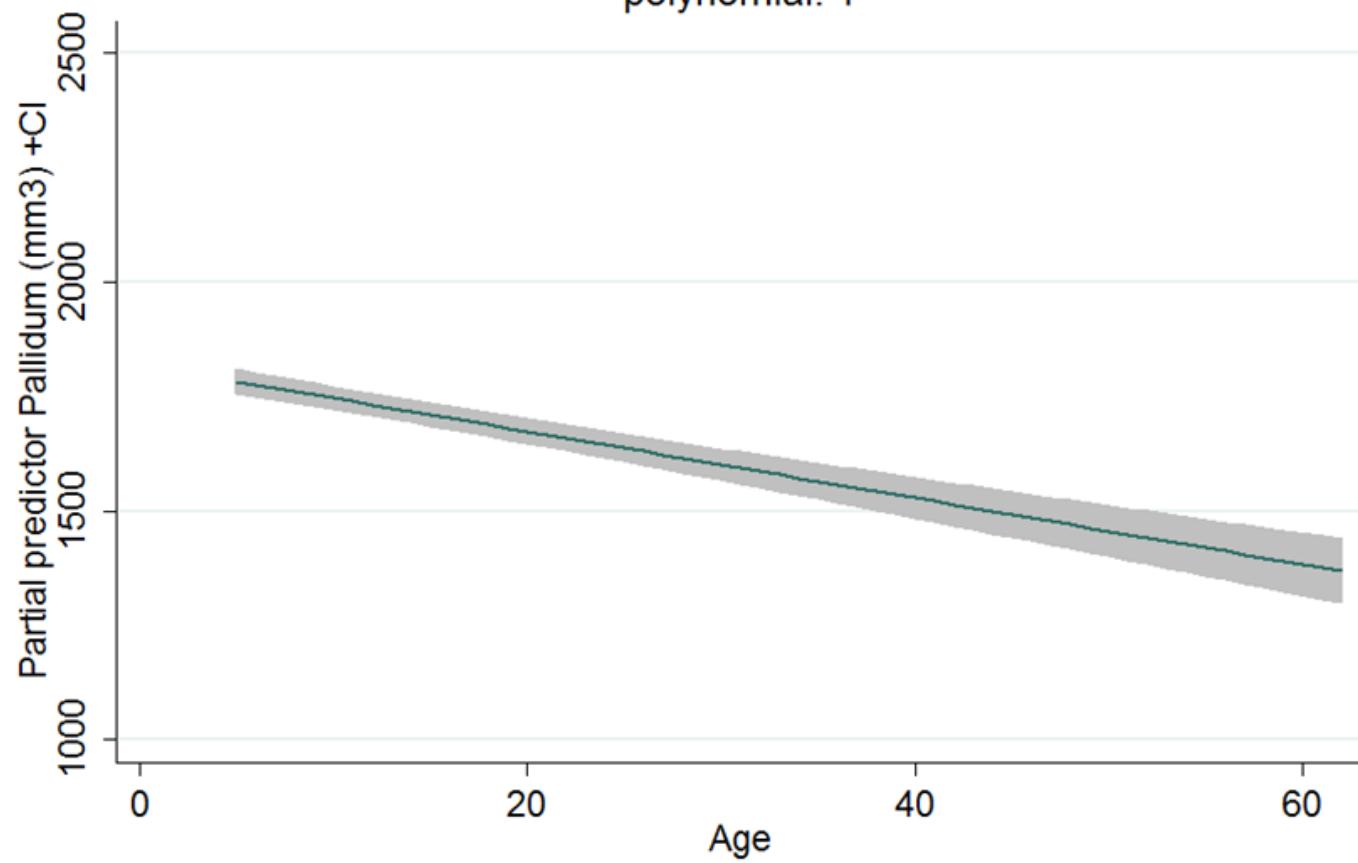
## Hippocampus Controls

Polynomial: 0, 0



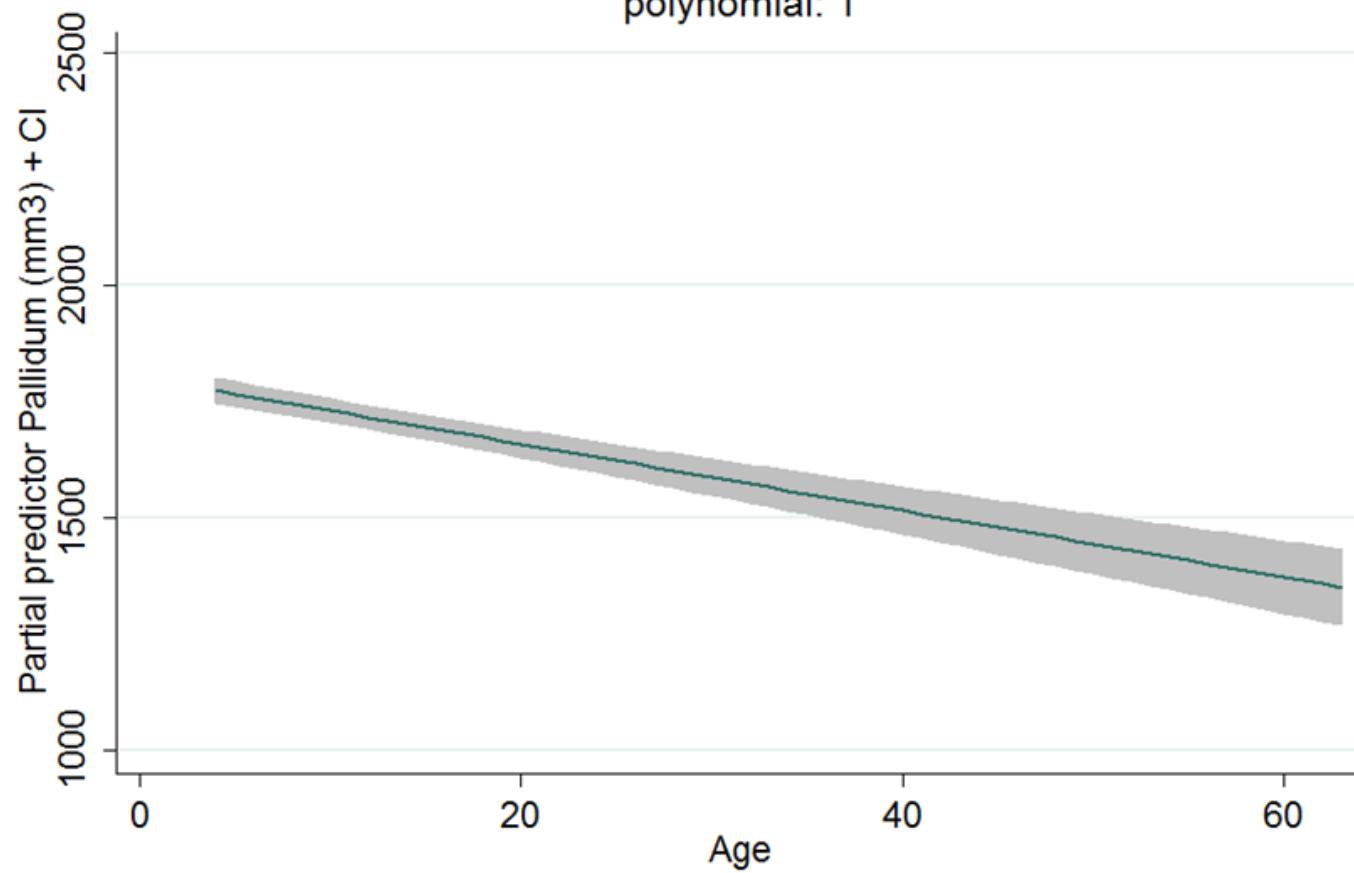
## Pallidum Cases

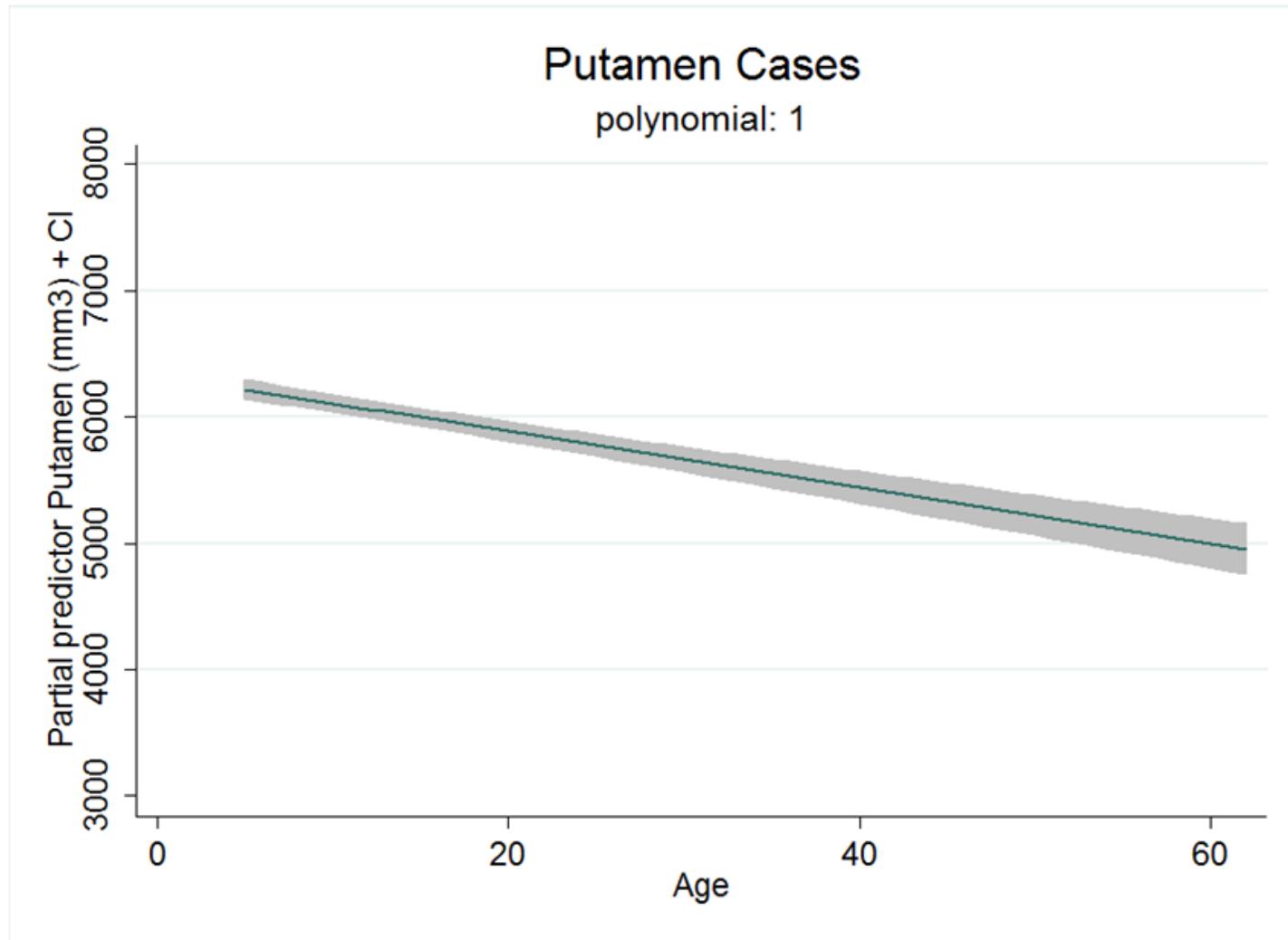
polynomial: 1



## Pallidum Controls

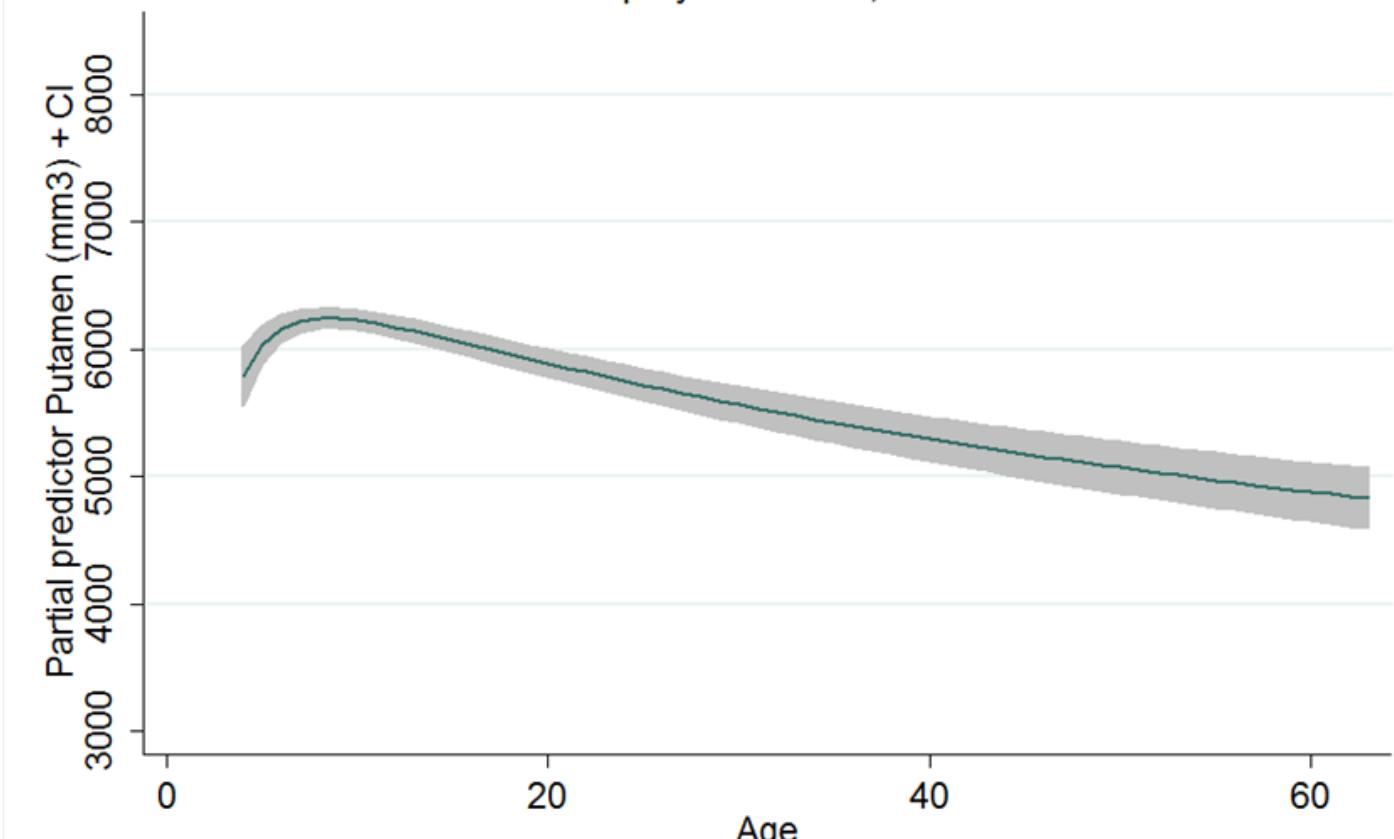
polynomial: 1





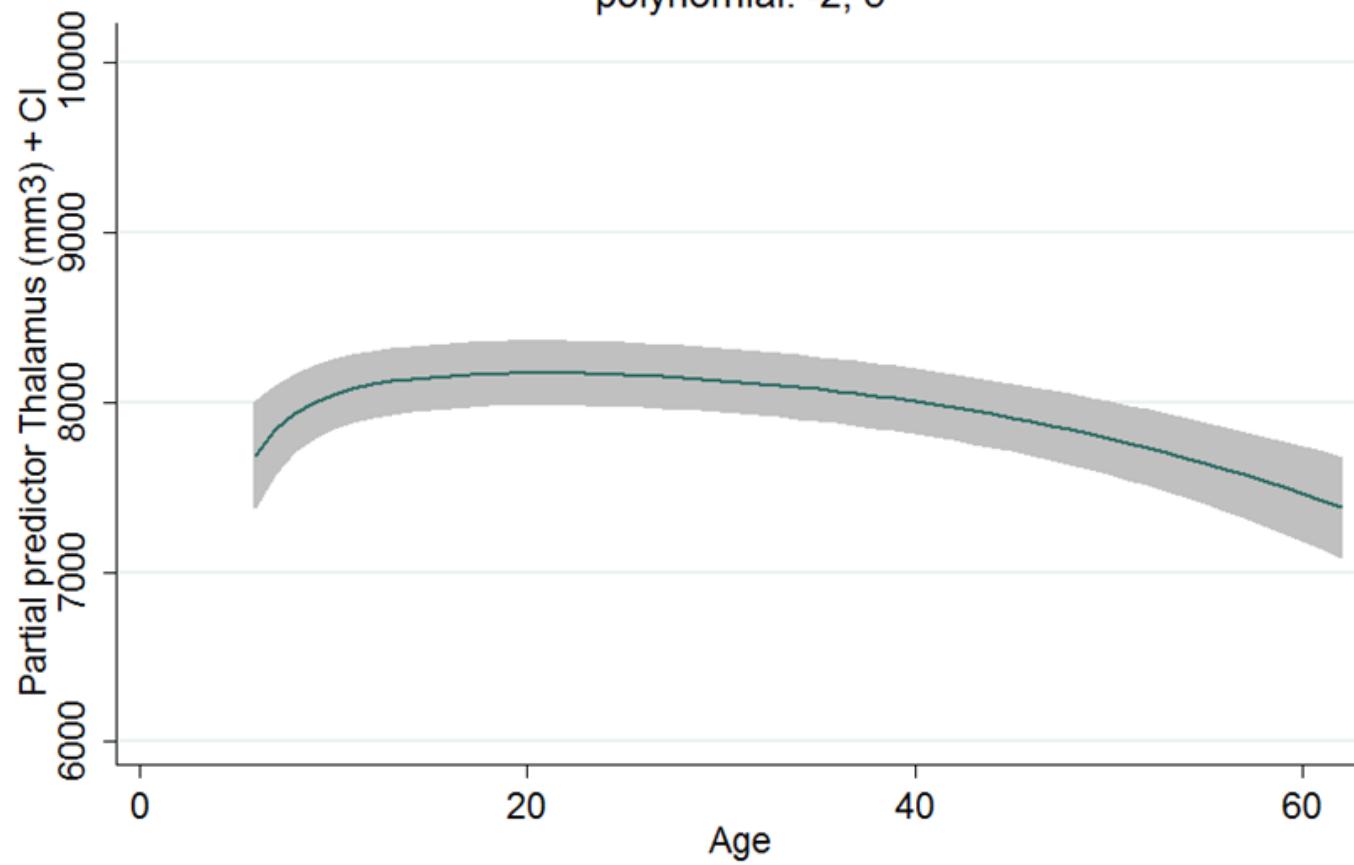
## Putamen Controls

polynomial: -1, 0



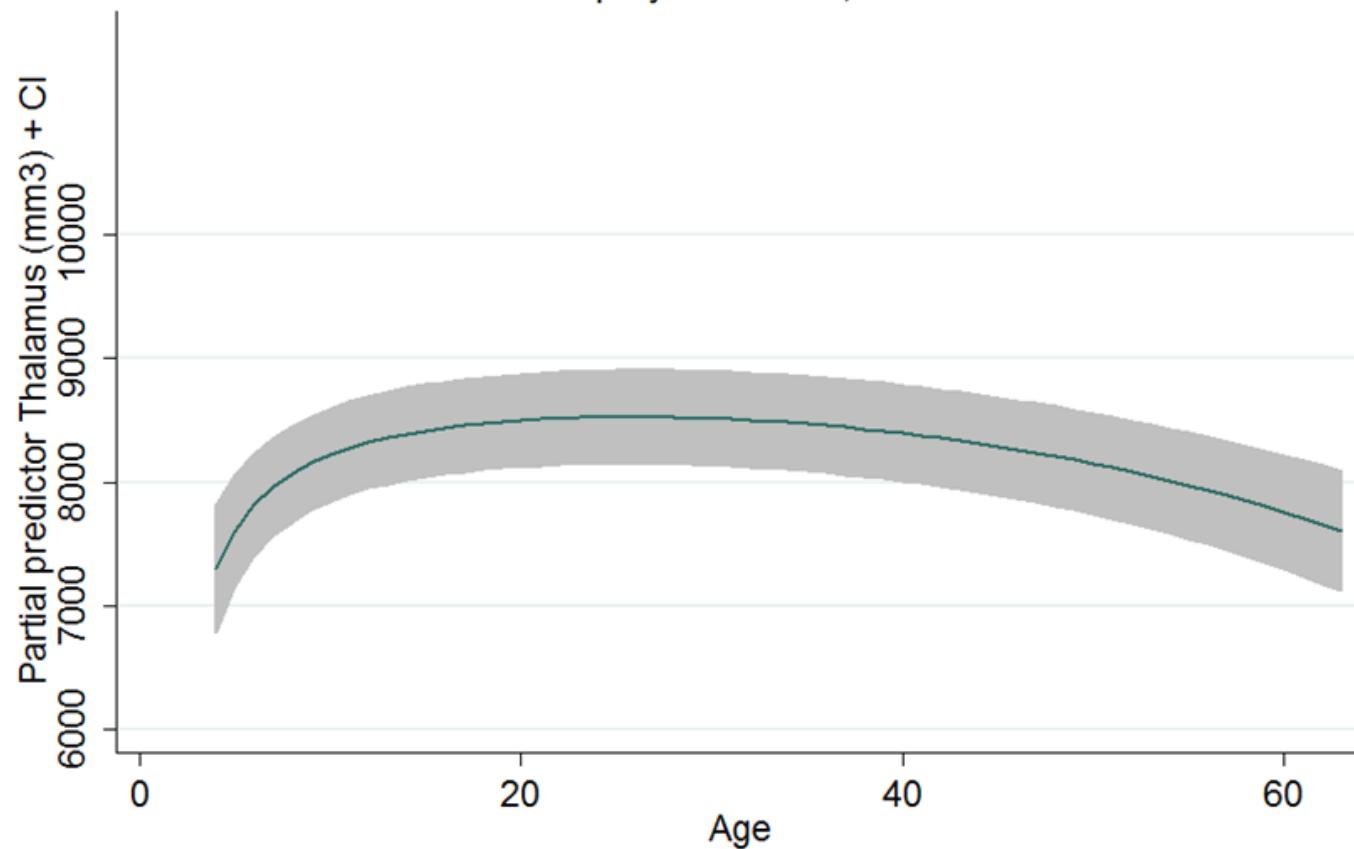
## Thalamus Cases

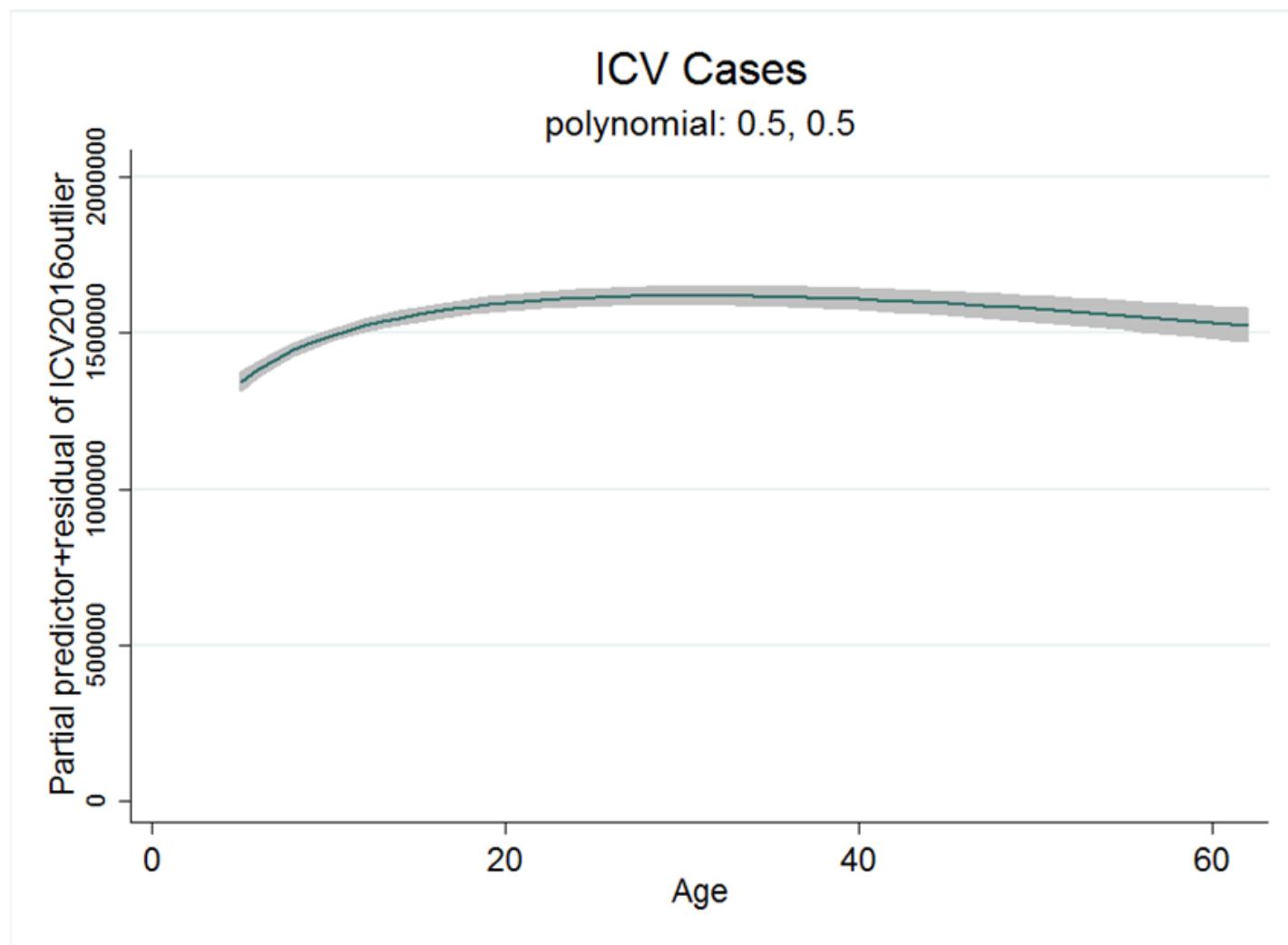
polynomial: -2, 3

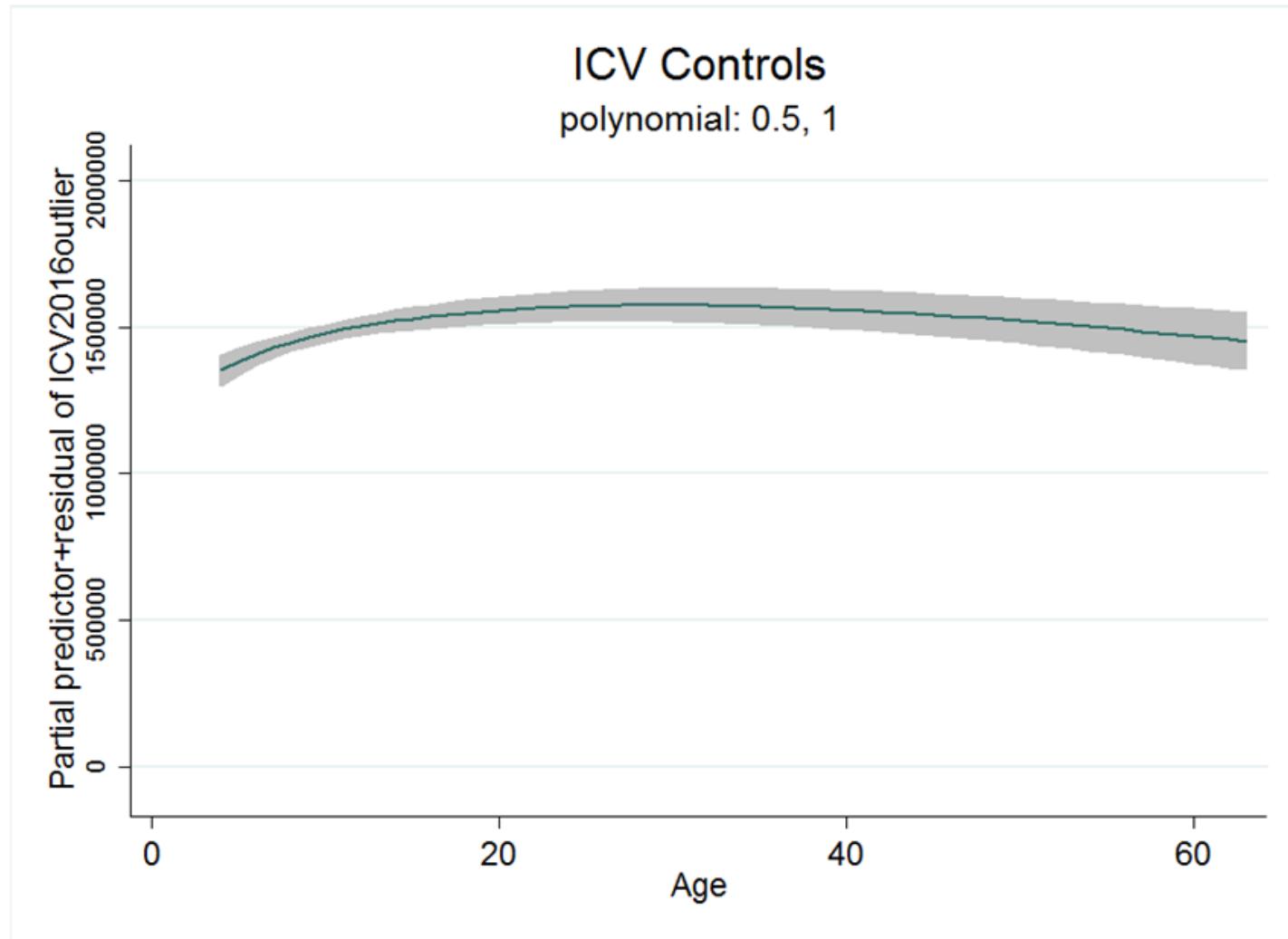


## Thalamus Controls

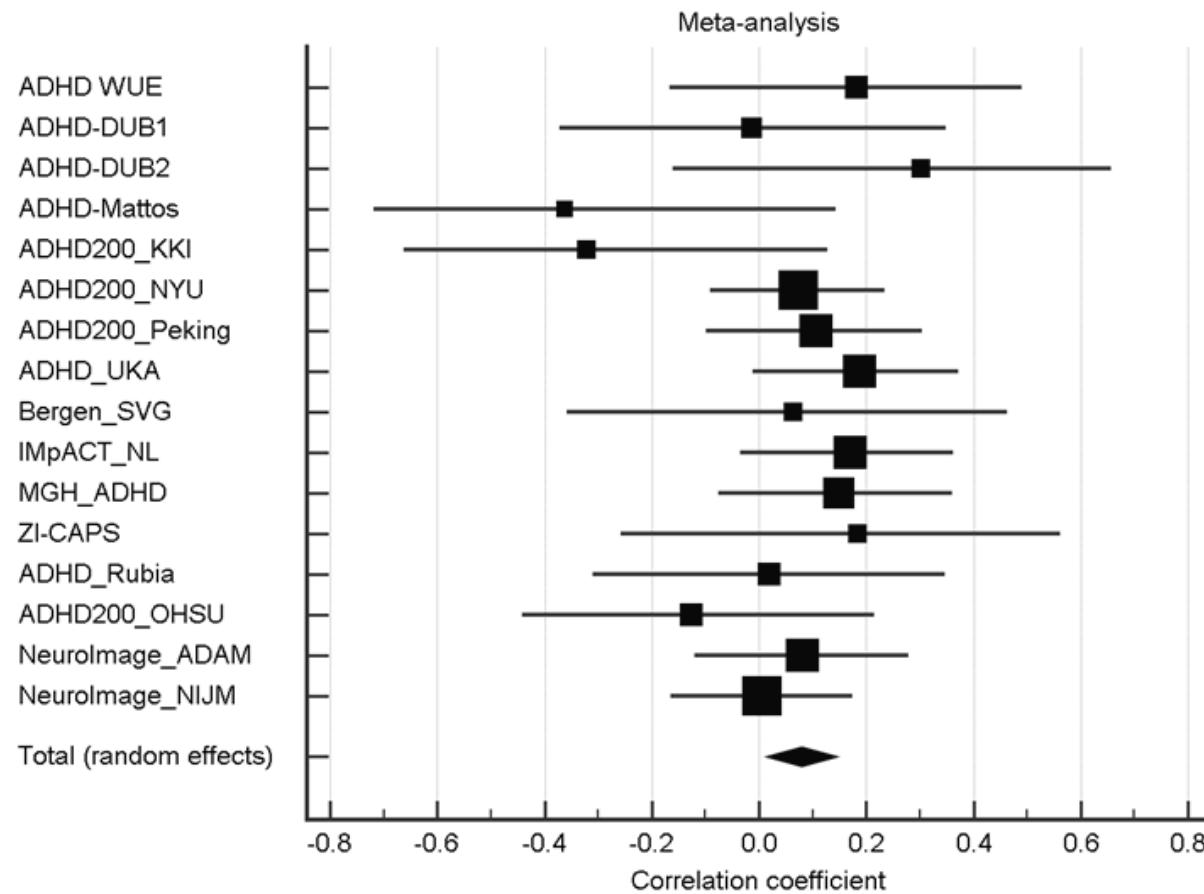
polynomial: -1, 3







**sFigure5.** Forest plot: result of the meta-analysis of the correlation between total number of ADHD symptoms and caudate volume.



Note: Displayed is the forest plot of the meta-analysis of the correlation between ADHD symptoms scores (Hyperactive/Impulsive + inattentive symptom scores) and caudate volume, controlling for age, sex and ICV.

## References

1. Viechtbauer W. Conducting meta-analysis in R with the metafor package. *Journal of Statistical Software* 2010; **36**(3): 1-48.
2. van Erp TG, Hibar DP, Rasmussen JM, et al. Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. *Mol Psychiatry* 2015.
3. Schmaal L, Veltman DJ, van Erp TG, et al. Subcortical brain alterations in major depressive disorder: findings from the ENIGMA Major Depressive Disorder working group. *Mol Psychiatry* 2015.
4. Harville DA. Maximum likelihood approaches to variance component estimation and to related problems. *Journal of the American Statistical Association* 1977; **72**(358): 320-38.
5. Nakagawa S, Cuthill IC. Effect size, confidence interval and statistical significance: a practical guide for biologists. *Biol Rev Camb Philos Soc* 2007; **82**(4): 591-605.
6. Sauerbrei W, Meier-Hirmer C, Brenner A, Royston P. Multivariable regression model building by using fractional polynomials: Description of SAS, STATA and R programs. *Computational Statistics & Data Analysis* 2006; **50**(12): 3464–85.